Long-term developmental impact of withholding parenteral nutrition in paediatric-ICU: a 4-year follow-up of the PEPaNIC randomised controlled trial

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Abstract (248/250)

Background: The PEPaNIC-RCT (Leuven-Rotterdam-Edmonton, N=1440 recruited from 2012-2015) showed that withholding parenteral nutrition for 1 week in critically ill children (late-PN), as compared with early supplemental PN (early-PN), prevented infections, accelerated recovery and improved neurocognitive development assessed 2-years later. As several neurocognitive domains can only be thoroughly assessed from 4-years of age onwards, the aim of the study was to determine the impact of late-PN versus early-PN on physical, neurocognitive, and emotional/behavioural development 4-years post-randomisation.

Methods: This is a pre-planned, blinded, 4-year follow-up study of PEPaNIC patients and of matched healthy children (ClinicalTrials.gov-NCT01536275). Studied outcomes were anthropometrics, health status, parent/caregiver-reported executive functions and emotional/behavioural problems, and clinical tests for intelligence, visual-motor integration, alertness, motor coordination and memory. Via multivariable linear and logistic regression analyses, after imputation for missing values (≤30%) and adjustment for risk factors, we investigated the impact of early-PN versus late-PN hereon.

Findings: Patients testable for neurocognitive development (356 late-PN, 328 early-PN) revealed worse anthropometric, health status, neurocognitive and emotional/behavioural developmental outcomes than 369 healthy controls. Outcomes of late-PN patients were never worse than those of early-PN patients. In contrast, late-PN patients had fewer internalising (β-estimate (95% confidence interval) -1·880 (-3·690 to -0·071), P=0.042), externalising (-1·731 (-3·433 to -0·028), P=0.046), and total emotional/behavioural problems (-2·442 (-4·215 to -0·668), P=0.007) than early-PN patients, which were normalised by late-PN.

Interpretation: Omitting early-PN use for critically ill children protected against emotional/behavioural problems 4-years post-randomisation. This further supports de-implementation of early-PN.

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Introduction

Critical illness in children is associated with impaired physical, neurocognitive and emotional/behavioural development, which often persists years after discharge from the paediatric intensive care unit (PICU) and hospital.[1,2] In the last decade, avoidable intensive care-related factors contributing to parts of this legacy have been identified. These include hyperglycaemia, phthalates leaching into the blood from indwelling medical devices, and the early use of parenteral nutrition (PN) in the PICU.[3-5] The multicentre randomised controlled "Paediatric Early versus Late Parenteral Nutrition in Critical Illness – PEPaNIC" trial showed that withholding PN for one week in the PICU (late-PN), as compared with initiating PN within 24 h after admission to supplement insufficient enteral nutrition (Early-PN), not only improved intensive care outcomes but also executive functioning, externalising behavioural problems and visual-motor integration, as assessed two years later.[5,6] This was found to be mediated by the prevention of adversely altered DNA-methylation status evoked by early-PN, in particular of 37 CpG-sites related to genes involved in brain development.[7]

A methodological limitation of the 2-year follow-up study of the PEPaNIC-RCT was the large proportion of patients included who were younger than 4 years when tested neurocognitively.[5] Indeed, the brain of children matures further during the first years of life and as a consequence assessment of most neurocognitive domains is only possible from 4 years of age onwards.[8,9] Also, during development, impairments in physical or neurocognitive domains that were observed at 2 years follow-up may persist or disappear, whereas other problems may emerge. Taken together, this warrants a physical, neurocognitive and emotional/behavioural assessment at a later time point after critical illness. We therefore performed a 4-year follow-up study of the PEPaNIC-RCT to assess health status, parent/caregiver-reported and clinically observed neurocognitive and emotional/behavioural outcomes of patients in comparison with matched healthy children and to investigate the impact hereon of late-PN as compared with early-PN.

Methods

Study design and participants

In the PEPaNIC-RCT, 1440 critically ill infants and children admitted to the participating PICUs (University Hospitals Leuven, Belgium; Erasmus-MC Sophia Children's Hospital, Rotterdam, The Netherlands; Stollery Children's Hospital, Edmonton, Alberta, Canada) had been enrolled from 2012 to 2015.[6] The study protocol has been published.[10] The current study represents the pre-planned 4 years follow-up of this RCT.[6]

As described previously,[5] during PICU-admission, parents or legal guardians of the patients provided consent to contact them for long-term follow-up testing. First, survival status was assessed by reviewing hospital notes, via the National Register or via contact with the general practitioner or referring paediatrician. After receiving a standardised information letter, PICU-survivors and parents/caregivers were contacted by phone to obtain consent for scheduling an appointment for the medical and neurocognitive assessment, either at the hospital or at the patient's home. For patients who could not be reached by phone, survival status was reassessed at the end of the study.

For comparison, 369 healthy control children, demographically matched to the patients for age and gender, were recruited to undergo identical medical and neurocognitive assessment. Apart from unrelated children, also siblings and relatives of the patients were included, to control as much as possible for genetic and socio-economic/environmental background. Healthy control children were only included if they were not previously admitted to a neonatal ICU or PICU, or admitted to the hospital for 7 days or more with need for an intravenous line. History of inborn chronic metabolic diseases requiring a specific diet, such as diabetes, and conditions that require home parenteral nutrition such as short bowel syndrome were additional exclusion criteria.

Parents or legal guardians, and when applicable also adolescents, gave written informed consent according to local regulations. The institutional review boards at each participating site approved this follow-up study (ML8052; NL49708.078; Pro00038098).

Procedures, randomisation and masking

After having obtained informed consent, children who were admitted to the PICU during the PEPaNIC-RCT were randomly allocated (1:1) to receive "early-PN", with PN initiated within 24 h after PICU-admission to supplement enteral nutrition whenever 80% of targeted calories per age and weight categories was not yet reached, or "late-PN", which meant that all PN was withheld for up to 1 week in PICU. For the late-PN group, this corresponded to no PN in the majority of children. When enteral nutrition covered ≥80% of calculated targets, supplemental PN was discontinued. Total macronutrient doses administered on each of the first seven days in PICU are shown in **Figure S1**. After one week, for both groups equally, PN could be administered if necessary. Enteral nutrition was initiated early for both groups equally, and all patients received intravenous micronutrients until fully enterally fed.

Outcome assessors of the 4-year follow-up study were physicians and experienced paediatric psychologists who had not been involved in the management of the patients during their stay in the PICU and who were strictly blinded for treatment allocation. Parents had not been masked during the time the child was treated in the PICU and were not actively informed about the initial PEPaNIC study results or the 2-year outcome results (the latter which became only available near the end of the inclusions in the 4-year follow-up study).[6]

Outcomes

As performed in the previous 2-year follow-up study,[5] at 4-year follow-up, head circumference, body weight and height were measured. A clinical neurological examination was performed to assess gross neurological abnormalities. Via a structured interview with the parents/caregivers, it was assessed whether the child had been diagnosed with a somatic or psychiatric illness, and/or had been admitted to a hospital for medical or surgical reasons during the past four years for healthy control children and during the four years following the index PICU-admission for patients. Neurocognitive testability was determined based on screening of the medical file or based upon clinical judgement prior to the start of the neurocognitive assessment by the physician/psychologist and confirmed by the parents/caregivers.

To score performance for a broad range of neurocognitive functions, validated, internationally recognised questionnaires and clinical tests with adequate normative data were used. Parent-reported questionnaires that were used included the Behaviour Rating Inventory of Executive Function[11,12] (executive functioning, T-scores, with mean

50 and SD 10) and the Child Behaviour Checklist[13,14] (emotional and behavioural problems, T-scores, with mean 50 and SD 10). On both questionnaires, higher scores indicate more problems. Clinical tests consisted of the age-appropriate versions of the Wechsler Intelligence Quotient Scale[15-17] (intelligence, standard scores, with mean 100 and SD 15), the Beery Developmental Test of Visual-Motor Integration[18] (visuomotor integration, scaled score, with mean 10 and SD 3), tasks of the Amsterdam Neuropsychological Task Battery[9] (ANT for children aged 4 years or older), and the Children's Memory Scale[8] (CMS for children aged 5 to 16 years). Tasks of the ANT consisted of ANT-Baseline Speed (alertness, reaction time) and ANT-Tapping (motor coordination, number of taps,). Tasks of the CMS that were used were CMS-Numbers (verbal short-term memory and working memory, scaled scores with mean 10 and SD 3), CMS-Word Pairs (short-term and long-term verbal memory, and recognition, proportion of correct responses ranging from 0 to 1), CMS-Picture Locations (short-term visual memory, proportion of correct responses), and CMS-Dot Locations (short-term and long-term visual memory proportion of correct responses). The CMS-Learning index represents learning abilities of the child (standard score, with mean 100 and SD 15). For the clinical tests, a higher score indicates better functioning, with the exception of ANT-Baseline Speed. The extended description of the questionnaires and of the clinical/neuropsychological test battery is available in **Methods S1**.

Statistical analyses

For patients who had been included in the PEPaNIC-RCT, and who were alive and testable 4 years later, we estimated a loss to follow-up of the PICU-survivors of about 30%, based on previous trials.[3,5] With this sample size, we calculated to have >80% statistical power to detect, with a certainty of >95%, clinically relevant differences between the two randomisation arms, in the same order of magnitude as previously reported.[3,5] For the healthy control group, a sample size of 369 allows to detect a minimally clinically relevant difference in IQ of four points and similar differences as previously reported[3,5] between healthy control children and patients for the other outcomes with a power of >80% and certainty of >95%.

Inability to fully complete the neurocognitive test battery may indicate poor neurocognitive function and thus introduce bias. Similar to what was done for the earlier 2-year follow-up study,[5] missing values were therefore imputed by chained equations, with use of all available data per individual (**Methods S2, Figure S2-S4**).[19] Imputation of data

for age-specific tests was only performed within the respective age group. Bias and instability of the imputation model was minimised by only including outcomes with ≤30% missing data.[19] The number of imputation models was set at 31 to avoid loss of statistical power (**Methods S2, Figure S2-S4**).[19]

Univariable comparison of the pooled data from the imputed models was performed with use of Fisher-Exact test, Student t-test or Wilcoxon rank-sum test as appropriate. Multivariable linear and logistic regression analyses were performed on the 31 imputed datasets with the pooled beta-estimates or odds ratios reported to investigate the differences in outcomes between patients and healthy control children, and to analyse the differences between patients randomly allocated to late-PN or early-PN during the PEPaNIC-RCT.[5] All multivariable analyses adjusted for covariates as prespecified in the statistical analysis plan and as performed in the 2-year follow-up study.[5,10] For the comparison of critically ill patients with healthy control children, the analyses adjusted for the baseline risk factors age, centre, gender, race, geographic origin, language, hand preference, history of malignancy, a predefined "syndrome" (**Methods S3**), and the educational and occupational status of the parents/caregivers (**Methods S4**). Additional adjustment for admission diagnosis, severity of illness upon PICU-admission (PIM3 and PeLOD), risk of malnutrition (STRONGkids), and parental smoking behaviour prior to PICU-admission was performed for the comparison between the late-PN and early-PN groups. Acute effects of the randomisation on acquisition of new infections and on the duration of hypoglycaemia, ventilatory support and stay in the PICU, could potentially mediate any long-term effect and thus further adjustment here for was done in the multivariable models. In addition, further adjustment was performed for other post-randomisation treatments that could theoretically play a role (duration of haemodynamic support, treatment with antibiotics, corticosteroids, opioids, benzodiazepines, hypnotics and α-2-agonists).

Statistical analyses were performed with use of R version 3.5.3, MICE versions 3.4.0 and 3.6.0, and JMP© version 14.0.0 (SAS Institute, Inc, Cary, NC). Two-sided P-values at or below 0·05 were considered statistically significant. As the studied developmental outcomes are not independent (**Methods S5, Figure S5**), correction for multiple comparisons was not performed in our primary analyses.[7,20] We did correct for multiple testing in a sensitivity analysis by computing permutation based adjusted p-values (**Methods S6**).

This trial is registered with ClinicalTrials.gov, NCT01536275.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit for publication. The corresponding author had full access to all data and had final responsibility for the decision to submit for publication.

Results

Sixty-six (9·2%) late-PN patients and 71 (9·8%) early-PN patients did not survive to 4-years follow-up (p=0·69) and for 18 patients, survival status was unknown (**Figure 1**). A total of 222 late-PN patients and 247 early-PN patients survived but declined participation or were not contactable (p=0·47). Hence, loss to follow-up was 33·8% (487/1440). At follow-up, 59 (8·2%) late-PN patients and 73 (10·1%) early-PN patients were too disabled for neurocognitive testing (p=0·21) and were excluded from the analyses. For transparency, any available clinical data and/or questionnaire results for these patients are provided in **Table S1**. Between March 8th 2016 and November 8th 2019, a total of 684 patients and 369 healthy controls underwent long-term neurocognitive testing and were included in the imputation models for subsequent multivariable analyses. Neurocognitive testing was performed at the hospital for 442 (64·6%) patients and 301 (81·6%) healthy controls (p<0·0001), with no differences in place of assessment between late-PN and early-PN patients (p=0·99). Demographics and medical characteristics of patients and healthy control children are shown in **Table 1**. Randomisation allocation and primary and secondary intensive care outcomes of patients who were tested at 4-year follow-up were overall comparable with the initial PEPaNIC study population.

In univariable and multivariable comparison, patients at 4-year follow-up had worse outcomes for height, weight and head circumference, for health status, clinically assessed neurological functioning, parent/caregiver-reported executive functioning and emotional and behavioural problems, clinical tests for intelligence, visual-motor integration, alertness, motor-coordination, and memory than healthy control children (**Table 2, Table 3**).

As compared with patients who had been allocated to early-PN, late-PN patients were comparable for height, weight, body mass index, and head circumference, and for clinically assessed neurological functioning in univariable and multivariable analysis (**Table 2, Table 3**). In univariable analyses, as compared with early-PN patients, fewer late-PN patients were admitted to hospital and parents/caregivers of late-PN patients reported significantly fewer internalising, externalising and total emotional and behavioural problems and problems regarding flexibility **(Table 2, Figure 2**). After adjustment for risk factors, internalising, externalising and total emotional and behavioural problems remained significantly less present in late-PN than in early-PN patients (**Table 3, Table S3**). In a sensitivity analysis with correction for multiple testing, total emotional and behavioural problems remained less present in late-PN than in early-PN patients with an adjusted p-value of 0·053 (**Figure S6**). For internalising and externalising problems as well

as total emotional and behavioural problems, late-PN patients were not different from healthy control children (**Table S4**).

Differences in intensive care outcomes of the randomised intervention and other post-randomisation factors overall did not explain the observed differences at 4-year follow-up (**Table S3**). Interestingly, treatment with benzodiazepines was independently associated with worse outcome, whereas α2-agonist use was associated with better outcome.

Discussion

Four years after critical illness, children were found to still suffer from an important legacy characterised by broad abnormalities in all investigated developmental domains such as growth, health status, and neurocognitive and emotional/behavioural functioning, a finding that confirmed earlier observations.[3] The omission of supplemental PN throughout the first week in the PICU did not harm physical and neurocognitive development and protected patients specifically against emotional/behavioural problems that were present in patients who received early-PN.

A first important finding was that the 4-year legacy of critical illness was still spanning all developmental domains. To what extent these abnormalities are acquired during PICU stay remains debated.[25] However, the developmental legacy documented 4 years after critical illness was found to remain present after adjustment for all known baseline risk factors upon PICU admission. The documented developmental abnormalities are relevant, as they are known to have direct implications for daily life and to hamper future societal perspectives.[2,26,27] Moreover, the developmental impairment after paediatric critical illness is at least as pronounced as what has been reported for children who survived cancer[28-30] and for children suffering from chronic diseases.[31,32]

Interestingly, part of this legacy, more specifically the emotional and behavioural problems at 4-year follow-up, was found preventable by omitting the use of early-PN in the PICU. These emotional and behavioural problems comprised internalising, externalising and other problems. Internalising problems are evidenced by anxious and depressive symptoms, and by social withdrawal.[13,14] These are the consequences of over-controlling behaviour. Externalising problems become apparent in aggressive and norm-deviant behaviour, and are the consequence of under-controlling behaviour that results in conflicts with others and in violation of social norms. In the total score for the emotional and behavioural problems, not only internalising and externalising behavioural problems, but also sleep problems for younger children and social, thinking and attention problems for older children are included. Such emotional and behavioural problems are thought to be in part a consequence of poor development of the executive functions, such as poor inhibitory control.[33,34] This could explain why, at 2-year follow-up, we found that not being exposed to early-PN predominantly reduced abnormal inhibitory control[5] whereas 2 years later, the impact on the emotional and behavioural problems became more apparent.

The developing brain of children thus appears vulnerable to metabolic insults during periods of critical illness. We previously showed that tight glycaemic control in PICU prevented impaired motor coordination 4 years after admission,[3] an impairment that was less apparent in the patients of the current study, who had received at least some form of blood glucose control in the PICU. In addition to avoiding pronounced hyperglycaemia, omitting parenteral nutrition early during critical illness was here found to further protect the normal development of other neurobiological pathways that coordinate emotions and behaviour. This indicates that the neurocognitive legacy of paediatric critical illness is multifactorial, and improvement can only be expected by a stepwise elimination of various causal factors. The stepwise elimination of harmful factors will need the support of clinical guidelines to help implementation or de-implementation of certain interventions, such as the latest ESPGHAN/ESPEN/ESPR/CSPEN guidelines on paediatric parenteral nutrition.[35] Nevertheless, even though certain progress has been made, this study showed that children who have been critically ill clearly still face important developmental problems. These findings thus highlight the need for setting up a structured post-critical illness follow-up consultation for these children, with referral to a specialised health care professional (e.g. clinical psychologist or psychiatrist) who can initiate an appropriate intervention when warranted.

This study has limitations to highlight. First, for the clinical tests that assess inhibition and flexibility, missing data for >30% of the population did not allow imputation and thus no information on differences between groups could be provided. Second, neuroimaging studies were not performed due to ethical and practical considerations. The strengths of the study comprise the limited loss to follow-up as compared with other long-term follow-up studies of PICU patients[36,37] and the broad assessment of the physical, neurocognitive and emotional/behavioural development of patients and matched healthy control children.

In conclusion, also 4 years after critical illness, an important physical, neurocognitive and emotional/behavioural legacy was documented. The omission of the use of early-PN in the PICU did not harm any of the developmental domains and specifically protected patients against emotional/behavioural problems that were no longer overrepresented in late-PN patients as compared with healthy controls. These data further support de-implementation of the use of PN early during critical illness in infants and children. The findings also open perspectives for future identification of other modifiable risk factors related to the intensive care management.

Research in context

Evidence before this study

The multicentre paediatric early versus late parenteral nutrition in critical illness (PEPaNIC) RCT showed that omitting supplemental parenteral nutrition during the first week in the PICU improved short-term outcome as compared with initiating parenteral nutrition early to reach caloric targets when enteral nutrition was insufficient. In view of concerns about potential harm induced by accepting substantial macronutrient deficits with regard to growth, health status, clinically assessed neurological functioning and emotional/behavioural development in the long term, a 2-year follow-up study of the PEPaNIC children was performed. This study showed that withholding parenteral nutrition during the first week of critical illness in children did not adversely affect survival, growth, health status and neurocognitive functioning, and actually improved parent-reported or caregiver-reported executive functioning (inhibition, working memory, meta-cognition and total executive functioning), externalising behavioural problems, and visual–motor integration as evaluated two years after PICU admission. However, specific concerns were raised for the substantially large group of critically ill children who were infants at the time of exposure to substantial macronutrient deficits. Although the infants benefitted the most from accepting early macronutrient deficits with regard to short-term outcome, it remained unknown whether they would be more at risk for adverse effects on long-term clinical, neurocognitive and emotional/behavioural outcomes. Because of their young age, these children could not be completely assessed neurocognitively at the 2-years follow-up of the PEPaNIC RCT.

We searched Medline Ovid, Embase, Cochrane Central Register of Controlled Trials and Web of Science up to November, 2019, with no date limits set, and without language restrictions, with different combinations of the search terms “nutritional support”, “parenteral nutrition or feeding”, “intravenous nutrition or feeding” AND “intensive care unit, “critical care”, “critical illness”, “intensive care”, “ICU”, “PICU” AND “long-term”, “neurocognitive or child development”, “child health or growth”. We found only one published long-term follow up study assessing the timing of parenteral nutrition during paediatric critical illness, which was the 2-year follow-up study of the PEPaNIC study.

Added value of this study

As children who were infants at the time of exposure to a substantial macronutrient deficit early during critical illness were too young for complete neurocognitive assessment at the 2-years follow-up of the PEPaNIC RCT, a 4-year follow-up study was warranted. In this 4-year follow up study of the PEPaNIC RCT, post-PICU survivors were still found to have impairments in all investigated developmental domains such as growth, health status, neurocognitive and emotional/behavioural functioning, as compared with healthy matched children. The omission of supplemental parenteral nutrition during the first week of PICU admission did not harm any of the physical and neurocognitive development domains and actually protected children specifically against parent-reported or caregiver-reported emotional and behavioural problems.

Implications of all the available evidence

Omitting the early use of parenteral nutrition in critically ill infants and children has not only shown to prevent ICU-acquired infections and to accelerate recovery, it was now also found to beneficially affect long-term neurocognitive development at 2 and 4 years post-randomisation. These short-term and long-term benefits strongly support the de-implementation of administering parenteral nutrition during the first week in the paediatric intensive care unit.

Contributions: GVdB, IVH, SV, KJ and KD designed the study. AJ, RE, JH, IV, KD, GGG, and PJW gathered data. SV, AJ, KD, RE, FG, IVH and GVdB analysed the data and wrote the manuscript, which was reviewed and approved by all authors. All authors jointly decided to publish. GVdB had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of interests: We declare no competing interests.

Data sharing: Data sharing is offered under the format of collaborative projects. Proposals can be directed to the corresponding author.

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Figure legends

Figure 1: Consort diagram of the study participants

Figure 2: Impact of late-PN versus early-PN in patients on long-term emotional/behavioural problems.

The figure represents the density estimates for total behavioural and emotional problems reported by parents or caregivers. Each line corresponds to an imputed dataset. Densities, which correspond to the proportions of children with a certain score (equivalent to a smoothed histogram), are shown separately for early-PN patients (red), late-PN patients (green) and healthy controls (blue). Higher scores indicate more total behavioural and emotional problems.