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Effect of Late versus Early Initiation of Parenteral Nutrition on Weight Deterioration during PICU Stay: Secondary Analysis of the PEPaNIC Randomised Controlled Trial

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Abstract

BACKGROUND AND AIMS Critically ill children are at increased risk of weight deterioration in the paediatric intensive care unit (PICU). Whether early initiation of parenteral nutrition (PN) prevents weight deterioration is unknown. The aims of this study were to assess the effect of withholding supplemental PN during the first week on weight Z-score change in PICU and to evaluate the association between weight Z-score change in the PICU and clinical outcome.

METHODS This is a secondary analysis of the Paediatric Early versus Late Parenteral Nutrition in Intensive Care Unit (PEPaNIC) randomised controlled trial (N=1440), which focused on the subgroup of patients with longitudinal weight Z-scores available on admission and on the last day in PICU. Patients were randomly allocated to initiation of supplemental PN after one week (Late-PN) or within 24 hours (Early-PN) when enteral nutrition was insufficient. The effect of Late-PN versus Early-PN on the change in weight Z-score was investigated, adjusted for risk factors. Moreover, the association between weight Z-score change and clinical outcomes was explored, adjusted for risk factors.

RESULTS Longitudinal weight Z-scores were available for 470 patients. Enteral nutrition intake was equal in the Early-PN and Late-PN group. Less weight Z-score deterioration during PICU stay was associated with a lower risk of new infections (adjusted OR per Z-score increase 0.72 [0.55-0.96], $p=0.02$), and with a higher likelihood of an earlier discharge from PICU alive (adjusted HR per Z-score increase 1.22 [1.10-1.37], $p<0.001$). During PICU-stay, the change in weight Z-score did not differ among both groups (Late-PN median 0.00 [-0.34-0.12] vs Early-PN median -0.03 [-0.48-0.01], adjusted $\beta=0.10$ [-0.05-0.25], $p=0.18$).

CONCLUSIONS Weight deterioration during the PICU stay was associated with worse clinical outcomes. Withholding supplemental PN during the first week did not aggravate weight Z-score deterioration during PICU stay.

TRIAL REGISTRATION [clinicaltrials.gov NCT01536275](https://clinicaltrials.gov/ct2/show/study/NCT01536275)

45 *KEYWORDS* Paediatric Intensive Care Unit; Parenteral Nutrition; Weight; Nutritional Status; Nosocomial
46 infections

Introduction

Critically ill children admitted to the paediatric intensive care unit (PICU) are at increased risk for deterioration of their nutritional status.[1-5] Although increased nutritional intake is associated with improved nutritional status, the role of parenteral nutrition (PN) is unknown. Recently, the “Paediatric Early versus Late Parenteral Nutrition in Intensive Care Unit (PEPaNIC)” randomised controlled trial showed that withholding supplemental PN during the first week of intensive care (Late-PN) resulted in, among others, fewer new infections and reduced the duration of PICU stay as compared with initiating PN at day 1 (Early-PN).[6] Since the nutritional intake was lower in the Late-PN group because of delaying PN, this strategy might have impacted the nutritional status of these children. Therefore, we aimed to investigate the effect of withholding supplemental PN for 1 week on the change in weight Z-score during PICU stay as compared with early initiation of PN, and whether weight Z-score deterioration during PICU stay is associated with worse clinical outcome.

Materials and Methods

Study design

This is a secondary analysis of the PEPaNIC randomised controlled trial in a subgroup of children with anthropometric measurements available on admission and on the last day in PICU. The trial was conducted at the University Hospitals Leuven, Belgium; Erasmus MC–Sophia Children’s Hospital, Rotterdam, Netherlands; and Stollery Children’s Hospital, Edmonton, AB, Canada between 2012 and 2015. The full study protocol has been reported previously, trial registration number is NCT01536275 (clinicaltrials.gov).[6, 7] Briefly, 1440 critically ill children (term newborns to 17 years old) were randomly assigned 1:1 to Late-PN or Early-PN, if enteral nutrition (EN) was <80% of target. Early administration of PN was standard of care at that time in the participating hospitals. Patients with a low risk of malnutrition on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) were excluded. Patients in the Late-PN group received a dextrose 5%/saline infusion to match the administered fluid of those in the Early-PN group. Initiation and

incline of EN and intravenous administration of micronutrients were similar in both groups. After the first week, patients in both groups received supplemental PN if EN was <80% of target. The institutional ethical review boards of the participating centres approved the study. Written informed consent was obtained from the parents or legal guardians.

Definitions and outcomes

Change in weight Z-score was calculated from admission to the last day in PICU. Weight was measured to the nearest 0.01 kg using calibrated scales. The broad age range of our patients did not allow us to use the same measure of weight Z-score for all children. Therefore, weight Z-score was defined as weight-for-age Z-score[8] in children <1 year old and BMI-for-age Z-score[8] in children ≥1 year old, as was done previously.[9] In neonates, birthweight-for-gestational age Z-scores[10] were used until the age of 7 days to account for physiologic weight loss during the first week of life. Clinical outcomes were the risk of new infections during PICU stay, and the likelihood of an earlier discharge from PICU alive, with the duration of PICU-stay censored at 90 days, and the duration of PICU-stay of non-survivors set beyond that of all survivors at 91 days, to account for mortality as a competing risk. Discharge from PICU was a priori defined as ready for discharge from PICU (i.e. no longer in need, or at risk, of vital organ support).

Statistical analysis

Variables are reported as proportions, mean ($\pm$ SD) or median (IQR) as appropriate. Proportions were analysed univariably using χ^2 test, means with *t*-test and medians with Mann-Whitney test. The associations between change in weight Z-score and the risk of new infections or the likelihood of earlier discharge from PICU alive were analysed using logistic regression and Cox proportional hazard analyses, respectively, adjusted for the baseline risk factors centre, age, diagnosis group (aggregated to 4 groups based on stratification groups), STRONGkids category, Paediatric Logistic Organ Dysfunction (PELOD) score,

Paediatric Index of Mortality 2 (PIM2) score, and weight Z-score on admission. The effect of Late-PN on change in weight Z-score was analysed using linear regression, adjusted for the baseline risk factors mentioned above. Sensitivity analyses were performed by analysing average change in weight Z-score per day in PICU and by analysing age groups <1 year and ≥1 year separately. Beta values (β), odds ratios (OR) and hazard ratios (HR) with corresponding 95% confidence intervals were calculated.

P-values ≤0.05 were considered statistically significant. All analyses were performed with IBM SPSS Statistics version 21. Z-scores were calculated with use of Growth Analyzer Research Calculation Tool version 4, and Fenton 2013 Preterm Growth Chart version 6.

Results

Anthropometric measurements on admission and at the last day in PICU were available for 470 Dutch children (Figure 1), equally divided between the randomisation groups and with similar baseline characteristics in the Late-PN and Early-PN groups (Table 1). The total caloric intake during the first week differed significantly between the treatment groups due to differences in PN, whereas enteral intake was similar between the groups, according to the trial protocol (Table 2). Patients who were included in the analyses differed from those not included: they were younger, had a higher proportion of children with a high STRONGkids score, a lower PELOD score, a higher proportion of emergency admission, comprised more respiratory diagnoses and less cardiac surgery, and a lower proportion of inotrope or vasopressor medication on admission (Table 1). There were no significant differences between the Dutch children who were included and excluded from the analyses (data not shown), which indicates that the observed baseline differences could be attributed to selection of centre rather than selection bias.

In the children included in this substudy, Late-PN reduced the risk of new infections compared to Early-PN (Late-PN 12.4% vs Early-PN 21.6%, $p=0.01$; adjusted OR 0.47 [0.28-0.79], $p=0.004$; Figure 2). The duration

of PICU stay was significantly shorter in the Late-PN group (median 4 days [3-9]) than in the Early-PN group (median 6 days [2-13]; $p=0.04$). Furthermore, the likelihood of an earlier discharge from PICU alive was higher among children in the Late-PN group than those in the Early-PN group (adjusted HR 1.30 [1.08-1.57], $p=0.005$; Figure 2).

Less weight Z-score deterioration during PICU stay was associated with a lower risk of new infections (adjusted OR per Z-score increase 0.72 [0.55-0.96], $p=0.02$; Table 3, Figure 2), and with a higher likelihood of an earlier discharge from PICU alive (adjusted HR per Z-score increase 1.22 [1.10-1.37], $p<0.001$; Table 4; Figure 2). The median change in weight Z-score from admission to the last day in PICU was not significantly different between the treatment groups (Late-PN median 0.00 [-0.34-0.12] vs Early-PN median -0.03 [-0.48-0.01], univariable $p=0.19$; adjusted β 0.10 [-0.05-0.25], $p=0.18$, Figure 2). Since the duration of PICU stay differed between the treatment groups, we additionally investigated the average change in weight Z-score per day in PICU, which was a median of 0.00 (-0.06-0.01) in the Late-PN group and 0.00 (-0.05-0.00) in the Early-PN group (univariable $p=0.50$; adjusted β 0.03 [-0.04-0.10], $p=0.35$). Change in weight Z-score within children aged <1 year was not different between the Late-PN and Early-PN groups (Late-PN median -0.01 [-0.39;0.08] vs Early-PN median -0.10 [-0.53;0.08], univariable $p=0.37$; adjusted β 0.04 [-0.13;0.20], $p=0.68$). Within children aged ≥ 1 year, we also did not find a difference in change in weight Z-score between Late-PN and Early-PN (Late-PN median -0.001 [-0.26;0.20] vs Early-PN median -0.002 [-0.33;0.003], univariable $p=0.28$; adjusted β 0.19 [-0.07;0.46], $p=0.16$).

Discussion

In this secondary analysis of the PEPaNIC trial we found, in the subgroup of children with available longitudinal anthropometric data, that less weight Z-score deterioration during PICU stay was associated with a lower risk of new infections and with a higher likelihood of earlier discharge from PICU alive. However, these associations should be interpreted with caution, as cause and consequence within these associations remains unclear (i.e. acquiring a new infection might lead to weight Z-score deterioration). Furthermore, withholding supplemental PN during the first week, and thus accepting low macronutrient intakes, did not affect weight Z-score during PICU-stay compared to early supplemental PN. The effect of supplemental PN on the change in weight has not been investigated with a randomised design before. In several observational studies, less nutritional intake during the first 2 weeks or during the entire PICU or hospital admission was associated with deterioration of the child's nutritional status.[2, 4, 11] However, due to the observational design of these studies, their results could be confounded. Moreover, in these studies, the total caloric intake from EN and PN was investigated. In our study, we found that withholding supplemental PN did not aggravate weight Z-score deterioration while it decreased the risk of new infections and reduced the duration of PICU stay.

These results question the value of weight Z-score change to guide the effect of nutritional therapy in the acute phase of critical illness. Possibly, weight Z-score deterioration could be considered an expression of illness severity. Consensus statements on diagnosing malnutrition recognise disease burden/inflammation to contribute to illness-related malnutrition, although the precise role of inflammation is not yet clear.[12, 13] In case of severe inflammation such as critical illness, an adaptive housekeeping process called autophagy is essential to control cell damage.[14] Early administration of nutrients, in particular of amino acids, was found to suppress autophagy.[15] In critically ill adults, a fasting response evoked by withholding supplemental PN resulted in more efficient activation of autophagy in muscles and reduced muscle weakness.[16] Hence, in critically ill patients in whom severe inflammation is present, increased artificial

166 nutritional support might not be able to prevent nutritional status deterioration. Instead, reduction of cell
167 damage during the acute phase of illness, even if a reduction of nutritional intake is necessary to achieve
168 this, might contribute to optimal muscle and lean body mass preservation.

169
170 Body weight might be distorted by oedema and fluid retention, and is therefore difficult to measure reliably in
171 the PICU setting, which warrants caution when interpreting these results. However, such inaccuracies in
172 weight measurements were likely similar in both groups of our study, due to the randomised design and equal
173 fluid administration. It would have been interesting to investigate changes in body composition or muscle
174 tissue between the two groups. Possible measurements of body composition could be dual X-ray
175 absorptiometry (DXA), bioelectrical impedance (BIA/BIS) or air plethysmography. However, all of these
176 measurements have some important disadvantages in critically ill children, such as the children have to be
177 stable enough to be transported, and in case of plethysmography should be awake and able to stand or
178 sit.[17, 18] Despite its limitations, BIA/BIS might be a promising technique for future research. Phase angle
179 measurements derived from BIS have recently been associated with nutritional status and clinical outcomes
180 in critically ill children.[19, 20] However, currently, the effect of nutritional therapies on change in phase angle
181 during PICU stay and the relation with clinical outcomes is unknown. Other measurements to estimate body
182 composition could be mid-upper arm circumference or skinfold thickness, which are both less influenced by
183 oedema than weight, and easy to obtain at the bedside.[21] Information on muscle wasting and structure can
184 be derived from muscle biopsies or imaging. In the EPaNIC study in critically ill adults, muscle biopsies taken
185 at day 8 showed that Late-PN allowed more efficient activation of autophagic quality control.[16] Moreover,
186 in participants of the EPaNIC study, CT images made at day 2 and day 9 showed that withholding
187 supplemental PN during the first week of critical illness did not affect muscle wasting but improved the quality
188 of the muscle, reflected by the decreased amount of adipose tissue within the muscle compartments.[22]
189 Whether these observations can also be applied to critically ill children in different age categories is unknown.

190 In critically ill children, it is difficult to detect an altered muscle structure. The reliability and accuracy of
191 ultrasonography to evaluate muscle wasting in critically ill children is questionable.[23, 24]

192
193 There are additional limitations to our study that need to be addressed. First, as this study comprised a
194 subgroup, there may be a selection bias. However, the observed baseline differences could be attributed to
195 selection of centre instead of selection bias. Furthermore, the Late-PN and Early-PN groups were comparable
196 at baseline. Therefore, we feel that the results regarding the effect of Late-PN versus Early-PN on the change
197 in weight Z-score are reliable. Nevertheless, caution is warranted when generalising these results. Second,
198 in this study, we presented short-term outcomes. Recently, the 2 years follow-up of the PEPaNIC patients
199 showed no differences in weight, height, body mass index and head circumference Z-scores between the
200 Late-PN and Early-PN groups.[25] Thus, also in the long-term, there seem to be no repercussions on growth
201 when PN is withheld during the first week.[25]

202
203 To conclude, in a large heterogeneous PICU population, weight deterioration during PICU stay was
204 associated with worse clinical outcomes. Withholding supplemental PN during the first week of critical illness
205 did not aggravate weight Z-score deterioration during PICU-stay.

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208

209 **Statement of authorship**

210 GVdB, IV, SV, and KJ were involved in conception and design of the PEPaNIC study. EvP, JH, KJ and SV
211 designed the protocol for this secondary analysis of the PEPaNIC study. EvP, SV, JH, and KD wrote the
212 statistical analysis plan and performed the statistical analyses. EvP, JH, KJ, SV, IV and GVdB interpreted
213 the results and wrote the manuscript. All authors approved the manuscript and agree to be accountable for
214 all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work
215 are appropriately investigated and resolved.

216

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293 Figure Legends

294

295 Figure 1 CONSORT flow diagram

296 PN = parenteral nutrition

297

298 Figure 2 Schematic overview of relations tested

299 All relations were tested separately and independent of each other. PN = parenteral nutrition

300