CORRESPONDENCE

Early versus Late Parenteral Nutrition in Critically Ill Children

TO THE EDITOR: The report by Fivez et al. (March 24 issue)[1] suggested superiority of delayed versus early parenteral nutrition, although delay resulted in more frequent episodes of hypoglycemia, which were correctly included as a secondary outcome. "Brief" episodes of hypoglycemia were considered clinically irrelevant, but this is not supported by the references provided.[2,3] In the study by McKinlay et al.,[2] patients were treated to maintain a blood glucose of at least 47 mg per deciliter (higher than the 40 mg per deciliter in the study by Fivez et al.), and only 47% of neonates had been admitted to a neonatal intensive care unit (ICU), indicating that they were relatively healthy. In the article by Mesotten et al.,[3] the number of neonates was not specified. Hypoglycemia has serious effects in neonates, in particular after (cerebral) hypoxia–ischemia,[4,5] and trivializing hypoglycemia carries a major risk of hypoglycemia-induced neurocognitive impairment.

The important study by Fivez et al. does not provide (neonatal) brain imaging and long-term neurodevelopmental follow-up and was not designed to study the effects of hypoglycemia on the neonatal brain. I am concerned about the safety of blood glucose levels of 40 mg per deciliter or lower in sick neonates.

Floris Groenendaal, M.D., Ph.D.
University Medical Center Utrecht
Utrecht, the Netherlands
f.groenendaal@umcutrecht.nl

No potential conflict of interest relevant to this letter was reported.

1. Fivez T, Kerklaan D, Mesotten D, et al. Early versus late parenteral nutrition in critically ill children. N Engl J Med 2016;374:1111-22.
2. McKinlay CJD, Alsweiler JM, Ansell JM, et al. Neonatal glycemia and neurodevelopmental outcomes at 2 years. N Engl J Med 2015;373:1507-18.
3. Mesotten D, Gielen M, Sterken C, et al. Neurocognitive development of children 4 years after critical illness and treatment with tight glucose control: a randomized controlled trial. JAMA 2012;308:1641-50.
4. Harteman JC, Groenendaal F, Kwee A, Welsing PM, Benders MJ, de Vries LS. Risk factors for perinatal arterial ischaemic stroke in full-term infants: a case-control study. Arch Dis Child Fetal Neonatal Ed 2012;97:F411-6.
5. Burns CM, Rutherford MA, Boardman JP, Cowan FM. Patterns of cerebral injury and neurodevelopmental outcomes after symptomatic neonatal hypoglycemia. Pediatrics 2008;122:65-74.

DOI: 10.1056/NEJMc1605395

TO THE EDITOR: Fivez et al. found superior outcomes with late as compared with early parenteral nutrition in critically ill children. In their trial, supplementary parenteral nutrition was provided for patients receiving less than 80% of their nutrient target enterally. However, estimation of the energy requirement on the basis of

THIS WEEK'S LETTERS

calculations does not accurately reflect the resting energy expenditure of children in a pediatric ICU.[1] Standard equations may overestimate resting energy expenditure, which is measured by indirect calorimetry. Consequently, critically ill children are at high risk for unintended overfeeding with cumulative energy excess.[2] If that is the case, the poor outcome in the early parenteral nutrition group may be related to caloric overfeeding.

Interruptions to nutritional support in critically ill children are common; in one prospective study, patients spent 42.4% of their time in the pediatric ICU without nutritional support.[3] In adult surgical patients, interruption of enteral nutrition has been associated with undesirable outcomes such as prolonged hospital and ICU lengths of stay.[4] Therefore, if the authors had reported information about nutrition interruption of the critically ill children in their study, the results might be more convincing.

Yousheng Li, M.D.
Yuhua Huang, M.D.
Nanjing University
Nanjing, China
liys@medmail.com.cn

No potential conflict of interest relevant to this letter was reported.

1. Havalad S, Quaid MA, Sapiega V. Energy expenditure in children with severe head injury: lack of agreement between measured and estimated energy expenditure. Nutr Clin Pract 2006; 21:175-81.
2. Mehta NM, Bechard LJ, Dolan M, Ariagno K, Jiang H, Duggan C. Energy imbalance and the risk of overfeeding in critically ill children. Pediatr Crit Care Med 2011;12:398-405.
3. Keehn A, O'Brien C, Mazurak V, et al. Epidemiology of interruptions to nutrition support in critically ill children in the pediatric intensive care unit. JPEN J Parenter Enteral Nutr 2015;39: 211-7.
4. Peev MP, Yeh DD, Quraishi SA, et al. Causes and consequences of interrupted enteral nutrition: a prospective observational study in critically ill surgical patients. JPEN J Parenter Enteral Nutr 2015;39:21-7.

DOI: 10.1056/NEJMc1605395

TO THE EDITOR: Fluid excess results in increased morbidity and mortality among critically ill patients,[1] particularly if they have respiratory failure.[2] The control group in the trial by Fivez et al. received 5% dextrose in saline to compensate for the volume of total parenteral nutrition. The total parenteral nutrition contained hypertonic dextrose (15%), which has a profound effect on insulin secretion. The serum insulin response to total parenteral nutrition is substantially higher than to enteral feeding in the critically ill adult, often exceeding 100 μU per milliliter.[3] Experimental data indicate that such levels of insulin have a profound antinatriuretic effect,[4] which causes fluid retention in the critically ill. Controlling for fluid intake alone is unlikely to have yielded a similar fluid balance in the two groups, which might have influenced outcomes. This possibility could be assessed by comparing fluid balance and changes in body weight between the groups. Future trials should consider severe sodium restriction, reduced fluid intake, or both in the early-parenteral-nutrition group to achieve a similar fluid balance in the study groups.

Bruce R. Bistrian, M.D., Ph.D.
Beth Israel Deaconess Medical Center
Boston, MA
bbistria@bidmc.harvard.edu

No potential conflict of interest relevant to this letter was reported.

1. Lowell JA, Schifferdecker C, Driscoll DF, Benotti PN, Bistrian BR. Postoperative fluid overload: not a benign problem. Crit Care Med 1990;18:728-33.
2. Rosenberg AL, Dechert RE, Park PK, Bartlett RH. Review of a large clinical series: association of cumulative fluid balance on outcome in acute lung injury: a retrospective review of the ARDSnet tidal volume study cohort. J Intensive Care Med 2009;24: 35-46.
3. McCowen KC, Ling PR, Friel C, et al. Patterns of plasma leptin and insulin concentrations in hospitalized patients after the initiation of total parenteral nutrition. Am J Clin Nutr 2002; 75:931-5.
4. DeFronzo RA, Cooke CR, Andres R, Faloona GR, Davis PJ. The effect of insulin on renal handling of sodium, potassium, calcium, and phosphate in man. J Clin Invest 1975;55:845-55.

DOI: 10.1056/NEJMc1605395

THE AUTHORS REPLY: We agree with Groenendaal that our study was not designed to investigate the effect of hypoglycemia on the neonatal brain and that hypoglycemia should not be trivialized. In fact, the risk of hypoglycemia — although brief and carefully treated in the Early versus Late Parenteral Nutrition in the Pediatric Intensive Care Unit (PEPaNIC) trial — is one of the reasons why a long-term neurocognitive follow-up study, 2 and 4 years after enrollment, is currently ongoing. In our previous randomized, controlled trial investigating the effect of tight glycemic control on morbidity and mortality in the pediatric ICU and on long-term neurocognitive development,[1,2] the proportion of neonates was similar to that in the PEPaNIC trial. Despite a high incidence of brief hypoglycemia with tight glycemic control among neonates (84% vs. 3% with usual care), the mor-

bidity and mortality benefit of glycemic control in the neonatal subgroup was even larger than in the subgroup of older children. There was also no harm for the neurocognitive development as documented 4 years later.[2]

Li and Huang argue that the harm induced by early parenteral nutrition might be related to overfeeding because caloric targets were based on age and weight rather than on indirect calorimetry. Figure S2 in the Supplementary Appendix (available with the full text of the article at NEJM.org) showed the total caloric intake per kilogram of body weight, which increased progressively over time, for the three body-weight and age categories requiring different targets: from day 4 onward, children weighing less than 10 kg received approximately 85 kcal per kilogram per day, children weighing 10 to 20 kg received approximately 65 kcal per kilogram per day, and children weighing more than 20 kg received approximately 40 kcal per kilogram per day. Hence, unintended overfeeding was unlikely because achieved caloric intake remained below the recommended dose.[3] Indirect calorimetry is currently not often used in daily practice.[4] Enteral nutrition was identical in the two study groups and hence cannot explain the differences in outcome.

Bistrian suggests that differences in fluid retention could have affected the outcomes. Although fluid retention is associated with risk of death from critical illness, the daily fluid balances were not different in the two study groups.

We would note that the PEPaNIC trial enrolled only severely ill children, as indicated by the average Pediatric Logistic Organ Dysfunction (PELOD) score of 21, and all were at medium or high risk for malnutrition, as evidenced by the scores on the Screening Tool for Risk on Nutritional Status and Growth. The benefit of withholding parenteral nutrition during the first week in the pediatric ICU was present across the range of PELOD scores. The children with the highest risk of malnutrition, as well as the critically ill neonates, were found to benefit even more from withholding parenteral nutrition.

Sascha Verbruggen, M.D., Ph.D.
Erasmus MC
Rotterdam, the Netherlands
Ilse Vanhorebeek, Ph.D.
Greet Van den Berghe, M.D., Ph.D.
KU Leuven University Hospital
Leuven, Belgium
greet.vandenberghe@kuleuven.be

Since publication of their article, the authors report no further potential conflict of interest.

1. Vlasselaers D, Milants I, Desmet L, et al. Intensive insulin therapy for patients in paediatric intensive care: a prospective, randomised controlled study. Lancet 2009;373:547-56.
2. Mesotten D, Gielen M, Sterken C, et al. Neurocognitive development of children 4 years after critical illness and treatment with tight glucose control: a randomized controlled trial. JAMA 2012;308:1641-50.
3. Koletzko B, Goulet O, Hunt J, et al. Guidelines on paediatric parenteral nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), supported by the European Society of Paediatric Research (ESPR). J Pediatr Gastroenterol Nutr 2005;41:Suppl 2:S1-87.
4. Kerklaan D, Fivez T, Mehta NM, et al. Worldwide survey of nutritional practices in PICUs. Pediatr Crit Care Med 2016;17:10-8.
DOI: 10.1056/NEJMc1605395

Risk of Stroke after Transient Ischemic Attack or Minor Stroke

TO THE EDITOR: Amarenco et al. (April 21 issue)[1] report that fewer cardiovascular events were seen after a transient ischemic attack (TIA) or minor stroke in the TIAregistry.org project than in previous studies involving other cohorts. This is welcome news. However, in contemporaneous and subsequent clinical trials,[2,3] the risks of stroke during the first 90 days after a TIA or minor stroke were between 5.9% and 11.7% — higher than the 3.7% risk reported by the TIAregistry.org investigators. The actual risks among these trial populations are even higher, since even though trial enrollment was restricted to within 24 hours after the onset of symptoms, most participants underwent randomization after more than 12 hours. Therefore, events that occurred during the early, highest-risk period after a TIA or minor stroke, but before randomization, were not fully captured. Indeed, TIAregistry.org participants who were evaluated sooner after the index event had a higher risk of recurrent ischemia than those evaluated later on.

Other differences between the TIAregistry.org project and these subsequent trials remain. For example, TIAregistry.org sites were specialized, high-volume centers, and patients were excluded