The fear of necrotizing enterocolitis versus achieving optimal growth in preterm infants—an opinion

ORNA FLIDEL-RIMON1,3, DAVID BRANSKI2,3 & ERIC S. SHINWELL1,3

1Department of Neonatology, Kaplan Medical Center, Rehovot, Israel, 2Department of Pediatrics, Hadassah Hospital, Jerusalem, Israel, and 3Hebrew University, Jerusalem, Israel

Abstract

Very-low-birthweight (VLBW) infants suffer marked growth delay despite well-intentioned efforts at combining enteral and parenteral nutrition. Fear of necrotizing enterocolitis (NEC) has traditionally influenced neonatologists toward delaying and progressing slowly with enteral feeding, while supporting the infant with parenteral nutrition. Current evidence suggests significant benefits of enteral feeding that is started early and advanced at rates of 20–35 ml/kg/d.

Conclusion: We conclude that fear of inadequate growth should replace the fear of NEC in guiding nutritional strategies for these infants.

Introduction

The goal of nutritional support of very-low-birthweight (VLBW) infants that has been proposed by the American Academy of Pediatrics Committee on Nutrition is the achievement of postnatal growth at a rate approximating that of the third trimester of intrauterine life [1]. However, when prospectively assessed in 1660 VLBW infants in leading neonatal centers between 1994 and 1995, most of the infants did not achieve the median birthweight of term infants by the time of discharge from the hospital [2]. Indeed, almost 90% had growth failure at 36 wk postmenstrual age, and 40% at 18–22 mo of age [3]. The magnitude of this deficit reflects the increased time to achieve full enteral feedings and to regain birthweight.

Despite adherence to current nutritional recommendations, almost all VLBW infants accumulate significant nutrient deficits during the first weeks of life, and this deficit can be directly related to subsequent postnatal growth retardation [4]. As these weeks represent a critical period for brain growth, this deficit may have profound long-term significance [5]. Indeed, in the highest risk group of infants with birthweight below 1000 g (extremely low birthweight; ELBW), infants who received enteral feeding before 10 d of age achieved significantly improved weight gain when compared with infants who began to feed later [6].

The socio-economic implications of extremely pre-mature birth are profound. For example, young adults who were born very prematurely have poorer educational achievements, fewer continue with post-high-school education, and more suffer from anxiety and depression [7]. Although neurological injury is a primary factor, it is likely that postnatal growth failure is a major contributor to these outcomes.

We will review the relative merits of enteral and parenteral nutrition in achieving optimal growth in these infants.

Enteral versus parenteral nutrition

In order to achieve the same weight gain postnatally as antenatally, a combination of enteral and/or parenteral nutrition (PN) is routinely used. Comparison of these modes suggests distinct advantages for the enteral route. Firstly, the potential for higher calori...
intake is better achieved by enteral feeding than by PN. Thus, in order to achieve the required caloric intake with total parenteral nutrition (TPN), high dextrose concentrations are needed, and these are often not well tolerated by very premature infants. Enteral feeding has been shown to improve growth, produce better nitrogen balance, and help maintain the intestinal barrier [8–10]. Specifically, enteral feeding has trophic effects on gut growth that are mediated either by the supply of essential nutrients or the stimulation of local mucosal growth factor expression and peptide hormone secretion or activation of neural pathways [11–13].

When neonatal piglets receive nutrition only via the parenteral route, reduced gut growth and atrophy are seen. These are associated with increased apoptosis and proteolysis, and decreased gut DNA, protein mass, cell proliferation, villous height, gut hormone secretion, and growth factors [13]. Studies in neonatal piglets have shown that enteral intake of at least 40–60% of the total intake is necessary to prevent gut protein loss and maintain normal growth [14].

Enteral feeding (EF) increases gut hormone secretion. Berseth compared gut hormone secretion and intestinal motor activity after the initiation of enteral feedings in VLBW infants [15]. A comparison was performed between infants in whom EF was started at age 3–5 d (early) and at 10–14 d (late). Early-fed infants had significantly higher plasma levels of gastrin and gastric inhibitory peptide, and they were able to tolerate full oral nutrition sooner. Early feeding enhanced the maturation of small intestine motor activity.

Intestinal lactase activity is incomplete in preterm infants. Early enteral feedings increase intestinal lactase activity, as was demonstrated in a group of 130 preterm infants born at 26–30 wk of gestation, in which a comparison was made between those with enteral feeding starting on day 4 of life and those in whom enteral feeding was delayed to day 15. Lactase activity was significantly increased in the early group, and the infants suffered fewer episodes of feeding intolerance [16].

Gastrointestinal barrier function is immature in the preterm neonate, and this may facilitate translocation of enteric bacteria and result in gut-derived septice mia. Circumstantial evidence suggests that bacterial uptake may be further enhanced by an alteration of host nutritional status [17]. Some studies have shown that intestinal permeability decreases over the first days of life, and it has been suggested that this rapid postnatal adaptation may be associated with early enteral feeding [18]. Also, when intestinal adherent bacteria and bacterial translocation were evaluated in breastfed and formula-fed neonatal rats, it was shown that the formula-fed pups were more susceptible than breastfed to bacterial translocation [19]. Current research approaches to the enhancement of intestinal barrier function may include the use of breast milk, probiotics [17], and the addition of IgA [20] or epidermal growth factor [21] to artificial formula.

Early hypocaloric enteral feedings had beneficial effects on indirect hyperbilirubinemia, cholestatic jaundice, and metabolic bone disease in VLBW infants [22]. The benefit accrued in the absence of an increased incidence of complications.

Conversely, PN is associated with increased risk for nosocomial infections, inadequate growth, intestinal mucosal atrophic changes, and liver insult and cholestasis [23].

Despite these convincing arguments, early enteral feeding is by no means universally adopted. The primary rationale for this policy of “bowel rest” is fear of necrotizing enterocolitis (NEC). This fear stems from the observation that over 90% of infants who develop NEC were receiving enteral feeding. However, in recent years, the fear of NEC has been balanced somewhat by the fear of TPN-associated sepsis, potential intestinal mucosal atrophic changes, cholestasis, and inadequate growth. This has resulted in the development of an alternative approach known as trophic or minimal enteral feeding (MEF) [24]. Using this method, small volume feeds of 0.5–1 ml/kg/h are begun within the first few days of life and increased slowly as the infant’s condition permits. This combines an attempt to overcome the lack of gastrointestinal stimulation during TPN with minimal stress to the sick infant. MEF has been tried successfully and without an increased risk for intestinal complications [25]. Since MEF has been initiated as early as the first 24 h of life [26], this may lend support to the concept of providing the neonate with significantly larger volumes of early enteral feeding. Thus, although MEF has achieved popularity, many centers have moved on to a policy of early enteral feeding where feeding is begun within 1–3 d of birth and advanced at rates of 20–35 ml/kg/d. Recently, we demonstrated, in a retrospective study of VLBW infants, that this policy was associated with reduced risk of nosocomial sepsis and with no increased risk for NEC [27].

The concept that early enteral feeding can reduce nosocomial infections is well established in the adult population, particularly in critical patients, after major surgery and after severe burns [28,29].

Another approach to the comparison between these feeding methods is to evaluate the risks that may be incurred in each. Approximately 5–12% of VLBW infants will develop NEC during their hospitalization, while nosocomial sepsis will develop in 15–38% [30]. In the group of infants of birthweight below 1000 g, up to 65% will have at least one episode of sepsis during hospitalization, while NEC is seen in 14% [30]. Although the risks of both NEC and sepsis are
not directly comparable, they are both associated with significant adverse neurodevelopmental outcome, visual impairment, impaired head growth, and lower Bayley scale scores [31,32].

The primary aim, therefore, must be to prevent both NEC and sepsis in these high-risk infants. The evidence available to date seems to suggest that early enteral feeding offers the best hope of achieving this laudable target.

How early is too early?

The withholding of feeding has been compared to early introduction of feedings in a number of controlled trials. Osterag et al. attempted to determine the optimal time for initiating enteral feeds in sick VLBW infants [33]. They found no difference in the incidence of NEC between early enteral feeding starting on day 1 of life as compared with starting on day 7 of life. Likewise, Davey et al. compared early (2 d) versus late (5 d) enteral feeding in VLBW infants and, likewise, found no difference in the incidence of NEC between the groups [34].

A systematic review of the results concluded that early introduction of feeding shortens the time to full feeds as well as the length of hospitalization without an increase in the rate of NEC [35,36]. Early was defined in this review as the first 4 d of life.

How fast is too fast?

This question has been extensively studied. It is more than 10 years since an extensive review of the issue concluded that we are trying to rediscover the proper use for enteral feeding. In particular, advancing feeds at a daily rate of up to 20–25 ml/kg/d was recommended [38]. However, despite this, many neonatologists continue to employ only minimal enteral feeding.

More recent studies of this question have shown that the incidence of NEC is unchanged when feeds are advanced at rates of 20, 30 or even 35 ml/kg/d [38,40].

On the other hand, a recent study that compared minimal enteral feeding with advancing at 35 ml/kg/d showed significantly less NEC in the group receiving minimal enteral feeding. The interpretation of this study, however, is complex as enteral feeds were introduced only at 10 d of life, which means that, in effect, this was a “bowel rest” strategy [41].

Irrespective of the rate of advancement, a recent study has suggested that standardized feeding protocols may prevent or minimize the risk for NEC [44]. Another unresolved issue that is beyond the scope of this review is the question of continuous versus intermittent bolus feeds. A recent study has provided evidence for improved growth with continuous feeding [43].

Economic impact of early enteral feeding

In our study mentioned above, starting enteral feeding at the age of 1–2 d instead of 5–8 d in VLBW infants was associated with an approximately 50% reduction in the incidence of sepsis without a change in the incidence of NEC [27]. Accordingly, the length of stay in infants with sepsis was 80 ± 43 d as compared with 52 ± 27 d in infants without sepsis (p = 0.0001). Likewise, the number of days on parenteral nutrition was 21 ± 12 d in infants with sepsis and 8 ± 6 d in infants without sepsis. Thus, early enteral feeding, by reducing sepsis and promoting accelerated growth, is likely to result in significant reduction of the hospital costs associated with very preterm birth. The long-term effects of this intervention on neurodevelopment are as yet unknown.

Summary

Enteral feeding in VLBW infants should be started early, as soon as the infant is stable, probably within the first 4 d of life, and should be advanced to full enteral feeds by between 1 and 2 wk of life.

The guiding principle for feeding these infants needs to shift from a fear of NEC to provision of optimal nutrition. The resulting improved growth and neurodevelopmental outcome may serve to reduce the social and economic burden that prematurity places on society.

References
