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Early nutritional support and outcomes in ELBW infants

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A B S T R A C T

Extrauterine growth restriction is a common finding among extremely low birth weight infants at discharge from neonatal intensive care units. It has been associated with significant caloric and protein deficits that accumulate during the hospitalization and with slower growth velocity observed with major neonatal morbidities. Recommendations to provide early nutritional support, both parenteral and enteral, have evolved in response to concern about the impact of poor in-hospital growth on growth and neurodevelopmental outcomes in early childhood. This paper will review the evidence supporting the provision of early nutritional support to extremely preterm infants by examining the outcomes associated with such practices.

1. Background

More than 60 years ago, Dancis et al. [1] commented that "the chief variable in determining the weight curve of … a premature infant is the feeding policy." Following that report, a number of studies [2–7] confirmed the strong influence of nutritional practices on growth. Infants who received parenteral nutrition for shorter periods of time, who were started on enteral feedings earlier, or who achieved full enteral nutrition sooner were noted to gain weight faster [5,7]. In another report, differences in the amount of calorie and protein intake provided to infants <30 weeks' gestation at 6 different neonatal intensive care units (NICUs) accounted for the largest difference in growth among infants [8]. However, since most of those studies reported results from the analysis of observational data, they were subject to a number of limitations. First of all, each infant's nutritional management was most likely influenced by the clinical team's impression of the infant's health. It is common practice that infants thought to be healthier might have been managed differently than infants thought to be less healthy; thus, enteral feedings might be initiated earlier or advanced more rapidly toward full enteral nutrition. Therefore, did the slower growth experienced by some infants result from nutritional practices that committed them to slower growth? Did the slower growth result from "suboptimal" nutritional support provided during the management of neonatal illnesses or due to the existence of the morbidities? This paper will review the evidence supporting the provision of early nutritional support to extremely preterm infants by examining the outcomes associated with such practices.

Several investigators have previously reported that the majority of infants managed with the nutritional support practices common until about 2000 were associated with postnatal or extrauterine growth restriction [EUGR [2,4,7]]. As displayed in Fig. 1, many of the infants born between 24 and 29 weeks' gestation remained less than the 10th percentile of a reference intrauterine curve [9], reflecting the initial period of weight loss and the delayed time before birth weight (BW) is regained. Furthermore, as shown by Embleton et al. [10], such growth is associated with significant caloric and protein deficits that begin to accumulate within the first weeks after birth and are difficult to recoup during the initial hospitalization, especially for infants less than 31 weeks' gestation.

The growth of VLBW infants who have experienced one or more major morbidity [for example, bronchopulmonary dysplasia (BPD), severe intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), or late-onset infection] or who expired before discharge has also been shown to be slower than the growth rate of infants who did not experience any of those morbidities and survived to discharge [7]. Those infants also regained BW later and thus, at 36 weeks' postmenstrual age (PMA) or discharge, their body weight would even be further below the median BW of a reference infant of similar PMA [9].

Finally, Ehrenkranz and co-workers [11] recently described the relationship between in-hospital growth velocity and neurodevelopmental and growth outcomes in 495 infants 501 to 1000 g BW whose in-hospital growth was monitored in the NICHD Neonatal Research Network's Growth Observational Study performed in 1994–95 [7] and who were evaluated at follow-up at 18 to 22 months' corrected age. The

Abbreviations: AGA, appropriate-for gestational age; BPD, bronchopulmonary dysplasia; BUN, blood urea nitrogen; BW, birth weight; CDC, Centers for Disease Control and Prevention; ELBW, extremely low birth weight; EUGR, extrauterine growth restriction; GA, gestational age; HC, head circumference; MRI, magnetic resonance image; NEC, necrotizing enterocolitis; NICHD, Eunice Shriver Kennedy Shriver National institute of Child Health and Human Development; NICU, neonatal intensive care unit; OFC, occiptiofrontal circumference; PMA, postmenstrual age; SDS, standard deviation score; SGA, small-for-gestational age; VLBW, very low birth weight.

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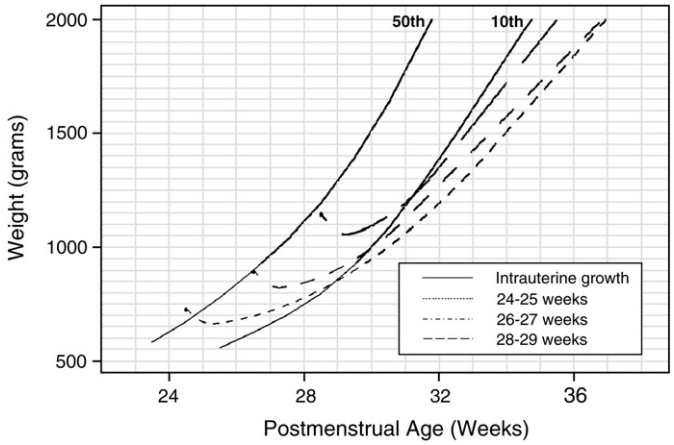

Fig. 1. Average body weight versus postmenstrual age in weeks for infants 24 to 29 weeks gestational age plotted with smoothed 10th and 50th percentile reference intrauterine growth curves [9]. The infants are stratified by gestational age, 24 to 25 weeks (short dashes), 26 to 27 weeks (medium dashes), and 28 to 29 weeks (long dashes). [Reprinted with permission [7]].

Table 1
Outcomes at 18–22 months corrected age by weight gain quartile.

Outcome	Quartile 1 ($n=124$)	Quartile 2 ($n=122$)	Quartile 3 ($n=123$)	Quartile 4 ($n=121$)	p-value[a]
Weight Gain (g/kg/d)	12.0 (2.1)[b]	15.6 (0.8)	17.8 (0.8)	21.2 (2.0)	–
Head Circumference [HC (cm/week)]	0.77 (0.2)	0.90 (0.2)	0.96 (0.1)	1.07 (02.)	–
Normal Neuro Exam (%)	70	77	76	86	<0.01
Cerebral Palsy (%)	21	13	13	6	<0.01
Mental Developmental Index (MDI)[c]	75.7 (18)	77.7 (18)	79.7 (18)	80.9 (15)	0.32
MDI < 70 (%)	39	37	34	21	<0.01
Psychomotor Developmental Index (PDI)[c]	74.8 (19)	77.5 (19)	81.5 (17)	83.3 (14)	<0.01
PDI < 70 (%)	35	32	18	14	<0.001
Neurodevelopmental Impairment [NDI (%)][d]	55	49	41	29	<0.001
Weight < 10th percentile (%)	58	61	51	46	0.03
Length < 10th percentile (%)	47	43	29	28	<0.001
HC < 10th percentile (%)	31	18	18	22	0.098

[Adapted with permission [11]].
[a] Kruskal-Wallis test for continuous variables; Mantel-Haenszel χ^2 or Fisher's exact test for categorical variables, as appropriate.
[b] Mean (S.D.).
[c] Bayley scales of infant development-II.
[d] Neurodevelopmental impairment was defined the presence of any of the following: any cerebral palsey, MDI < 70, a PDI < 70, deaf/severe hearing loss requiring bilateral amplification, or bilaterally blind.

study cohort was divided into quartiles of in-hospital growth velocity rates, and as the rate of weight gain increased between quartile 1 and quartile 4, from 12.0 to 21.2 g/kg/d, the incidence of neurodevelopmental impairment significantly decreased (Table 1). Significantly fewer infants in the highest quartile had anthropometric measurements at 18 months' corrected age below the 10th percentile values of the Centers for Disease Control and Prevention (CDC) 2000 growth curves (Table 1) [12]. Logistic regression analyses, controlled for potential demographic and clinical co-founders, and adjusted for center, suggested that in-hospital growth velocity rates exerted a significant, and possibly independent, effect on neurodevelopmental and growth outcomes at 18 to 22 months' corrected age.

Therefore, the obvious question is the extent to which changes in early parenteral and enteral nutritional support practices will result in improvements in growth and neurodevelopmental outcomes. A number of reports, derived from both observation studies and randomized, controlled trials [6,13–20], have described the benefits of combined early parenteral and enteral nutritional support, demonstrating that an aggressive nutritional regime could be provided to critically ill VLBW infants and would improve growth without increasing the risk of adverse clinical outcomes. In order to reflect the incremental contributions that result from the published reports of those studies, these papers will be primarily reviewed in the order of their publication.

2. Observations from studies of early parenteral and enteral nutritional support

The available evidence supporting the initiation of parenteral protein (i.e., amino acids) within hours of birth of extremely preterm infants, at minimum of 1.5 g/kg/d, but preferably at 3.0 g/kg/d, and then advancing to 4 g/kg/d, have been recently reviewed [21–24]. Most studies have shown that the early, aggressive administration of amino acids is well-tolerated and promotes a positive nitrogen balance and improved glucose tolerance without causing clinically significant alterations in metabolic acidosis, blood urea nitrogen (BUN) levels, plasma ammonia levels, or plasma amino acid levels. Although this has become a recommended practice, two recent reports [25,26] have raised a note of caution. In the first study [26] infants <30 weeks' gestation were randomized to a maximum of 2.5 g/kg/d of amino acids ($n=58$) or a maximum of 3.5 g/kg/d of amino acids ($n=64$). Blood levels of several amino acids were elevated on postnatal day 7 in the 3.5 g/kg/d group compared to the 2.5 g/kg/d group; no difference in growth rate (g/kg/d) was found at postnatal day 28. In the other study Blanco et al. [26] reported that an early, higher parenteral amino acid strategy was associated with peak BUNs > 60 mg/dL in 20% (6/30) of study patients who received 2 g/kg/d of amino acids shortly after birth, advancing to 4 g/kg/d by 1 g/kg/d increments. No infants in the control group who received 0.5 g/kg/d of amino acids beginning between 24 and 36 h of age, advancing by 0.5 g/kg/d to 3 g/kg/d experienced such elevated BUN levels. The elevated BUN levels led to a short-term restriction in the amino acid infusion provided to those patients.

The available evidence supporting the initiation of enteral feedings within the first several days of birth in extremely preterm infants has also been recently reviewed [21,24]. The available clinical trials have also been subject to several meta-analyses [27–29]. Although each of the meta-analyses concluded that a large, multicenter randomized controlled trial was still needed to determine how the risk of NEC was influenced by practices related to the initiation and advancement of minimal enteral feedings, parenterally-fed infants who received minimal enteral feedings initiated by 5 days of age were generally found to have significant reductions in the days to regain BW, the days to reach full enteral feedings, and the length of hospital stay, without a significant effect on the incidence of NEC. In fact, a recent prospective, observational study demonstrated that a risk factor for progression from medical NEC to severe (surgical) NEC was never having received any enteral feedings [30]. Therefore, the early initiation of enteral feedings is also a recommended practice.

Since the available evidence supports the early initiation of parenteral and enteral nutritional support, this paper will focus on reports describing the outcomes of combined early parenteral and enteral nutritional support. As noted above, since earlier reports may influence later studies, these papers will be primarily reviewed in the order of their publication.

A randomized, controlled trial performed by Wilson et al. [13] between 1990 and 1992, randomized 125 “sick” VLBW infants to an “aggressive” nutritional intervention group ($n=64$) or a control group ($n=61$). For infants in the intervention group, amino acids were initiated on the first day of life at 0.5 g/kg/d and lipids were initiated on the second day of life at 0.5 g/kg/d, both of which were increased to 3.5 g/kg/d by 0.5 g/kg/d increments; minimal enteral feedings, usually human milk, were initiated at 0.5 mL/h on day 1 and advanced as