

# Nutritional practices and postnatal growth restriction in preterm newborns

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## SUMMARY

**Objective:** to assess the nutritional practices in neonatal intensive care units (NICU) associated with growth retardation in premature (preterm) infants.

**Methods:** retrospective study of preterm infants weighing between 500 and 1,499g admitted to NICU. Evolution of growth and parenteral (PN) and enteral (EN) nutrition practices were analyzed.

**Results:** among 184 preterm infants divided into G1 (500 to 990g; n=63) and G2 (1000 to 1499g; n=121), 169 received PN (G1=63, G2=106). Compared with the recommendations, PN was started late, its progress was slow and the maximum glucose, amino acid, lipid and energy supplies were low in both groups. The initial supply of amino acid and lipid and initial and maximum glucose and energy were lower in G1. The onset of EN was early (1-2 days), the time to reach exclusive EN was appropriate (11-15 days) and the use of human milk was possible in a reasonable amount of time (7-13 days). The multivariate analysis showed that respiratory distress syndrome and obtaining a supply of 120 kcal/kg/day too late increased the chance of weight loss greater than 10%. Sepsis, maximum energy supply for PN <60 kcal/kg/day and obtaining a supply of 120 kcal/kg/day too late increased the chance of regaining birth weight after 14 days, while small for gestational age (SGA) at birth reduced this chance. SGA at birth, sepsis and achieving exclusive enteral nutrition after 14 days increased the chance of being SGA at post-conceptual age of term.

**Conclusion:** improving nutritional practices in the NICU can reduce the growth deficit in premature infants of very low birth weight.

**Keywords:** premature, enteral nutrition, parenteral nutrition, very low birth weight.

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## INTRODUCTION

Postnatal growth is an important predictor of growth and development throughout childhood in preterm infants<sup>1-3</sup> but despite knowing the importance of optimizing growth rates in the neonatal period, reducing the rate of extra-uterine growth restriction is still one of the great challenges for neonatal intensive care units (NICU).<sup>4-6</sup> The difficulties in providing adequate nutritional support in the hospitalization phase<sup>7-11</sup> of newborns with very low weight is one of the main reasons for this postnatal growth deficit.

A study to assess the nutritional practices adopted by four neonatal intensive care units, with different levels of

complexity and dimensions, showed that after analysis and adaptation of the routines of each center to the recommendations established in the literature, there was a reduction in the number of days for starting parenteral and enteral nutrition, a shorter time for achieving exclusive enteral nutrition and an energy supply of 120 kcal/kg/day, reduced length of hospital stay, and reduced percentage of children with weight below the 10<sup>th</sup> percentile upon discharge.<sup>1</sup>

The objective of this study was to assess the nutritional practices in a NICU and their relationship to the growth of preterm newborns during hospitalization.

## METHODS

This was a retrospective analysis of the medical records of premature infants born between January 2000 and December 2005 in a public teaching hospital. Preterm infants with birth weight (BW) between 500 and 1,499 g admitted to the neonatal intensive care unit at Hospital São Paulo were considered eligible. The exclusion criteria were death  $\leq 7$  days, major congenital anomalies and genetic syndrome. The study was evaluated by the Ethics Committee of the Universidade Federal de São Paulo, which considered signing the informed consent form unnecessary.

The data included about the newborns were gestational age, sex, birth weight, small for gestational age (SGA) characterized as birth weight below the 10<sup>th</sup> percentile (Alexander et al, 1996)<sup>12</sup> and resuscitation in the delivery room. The morbidities analyzed were respiratory distress syndrome (RDS), sepsis, necrotizing enterocolitis (NEC), patent ductus arteriosus (PDA), peri-intraventricular hemorrhage (PIVH) grades III and IV, bronchopulmonary dysplasia (BPD) and frequency of SGA at post-conceptual age of term (weight below the 10<sup>th</sup> percentile).

The drugs and procedures analyzed were use of surfactant, indomethacin, corticosteroids, mechanical ventilation and central venous catheter.

Bodyweight was recorded daily in accordance with the recommended standards. The maximum percentage of weight loss, time to regain birth weight, daily weight gain after recovery of birth weight and the number of days to reach 1800 grams were calculated.

Nutritional data were recorded daily and included the period between birth and a weight of 1800 g. For parenteral nutrition (PN) the start date, duration, and maximum initial supply of glucose, protein, lipid and energy were collected. For enteral nutrition (EN), characterized by infusion of the diet via gastrostomy tube, the type of diet, start date and number of days of minimal enteral nutrition use ( $\leq 10$  mL/kg/day, without increments), days to achieve exclusive enteral nutrition and energy supply of 120 kcal/kg/day were recorded.

Nutritional therapy was prescribed by the attending physicians, according to routine of the neonatal intensive care unit during the study period. PN and EN should be initiated within the first 48 hours of life. The recommendations established for PN were 80 kcal/kg/day of energy, maximum initial supply of glucose 6 g/kg/day and 16 to 18 g/kg/day, respectively; amino acids and lipids starting within 48 hours of birth and initial doses, increments and maximum supply of 1.0, 1.0 and 3.5 g/kg/day of amino ac-

ids and 0.5 to 1.0 g/kg/day, 0.5 to 1.0 g/kg/day and 3.0 g/kg/day of lipids, respectively.

Minimal enteral nutrition could be initiated within the first 48 hours of life and the progression to exclusively enteral nutrition was performed according to the clinical status of the child, with increments of 20 mL/kg/day in volume. Human milk was only to be used where possible, and formula for preterm infants when breast milk was not available. The use of additives to human milk started when human milk volume reached 100 mL/kg/day.

The numerical variables were expressed as median and range, and compared using the Mann-Whitney U test, or the mean and standard deviation, compared using the Student's t test. The categorical variables were expressed as numbers and percentages, and compared using the chi-square or Fisher's exact test.

To assess the factors associated with the percentage of weight loss, time to regain birth weight and frequency of small children for post-conceptual age, a logistic regression model was created using the variables with p value  $< 0.15$ . The statistical analysis was performed using Stata 10.0 software. Statistical significance was set at 5% ( $p < 0.05$ ).

## RESULTS

During the study period, 305 preterm infants with birth weights between 500 and 1,499 g were admitted to the NICU at Hospital São Paulo. One hundred and one of these were excluded: 87 for death  $\leq 7$  days, 11 for major congenital malformations and 3 for not using PN and EN. Twenty medical records were not located, although some of the data was available. The study group and the group with incomplete information were similar according to the perinatal variables, but the use of central venous catheter was higher ( $p = 0.001$ ) in the group with incomplete information (7 vs. 37.5%).

The 184 newborns were divided into two subgroups according to birth weight: group (G1) – 500 to 999 g ( $n=63$ ) and group (G2) – 1,000 to 1,499 g ( $n=121$ ). Except for gender, all clinical variables were different between subgroups (Table 1).

The infusion of glucose began within the first hours of life in all patients. PN was administered in 169 (92%) newborns (63 in G1 and 106 in G2) and their characteristics are shown in Table 2.

The number of children receiving amino acids within the first 48 hours of life, between 48 and 72 hours and after 72 hours were, respectively, 36 (57.2%), 14 (22.2%) and 13 (20.6%) in G1, and 54 (50.9%), 31 (29.2%) and 21 (19.9%) in G2, while the ones receiving lipids in these periods were, respectively, 36 (57.2%), 14 (22.2%) and 13

**TABLE 1** Characteristics of the newborns in the hospitalization period.

	Group 1 (n=63)	Group 2 (n=121)	p
Gestational age (weeks)	27.7±2.1	30.6±2.2	0.000
Male	25 (39.7%)	66 (54.5%)	0.055
Birth weight (g)	798.2±142.4	1258.3±137.1	0.000
SGA	13 (20.6%)	43 (35.5%)	0.037
Resuscitation in the delivery room	53 (84.0%)	60 (49.6%)	0.000
RDS	37 (58.1%)	35 (28.9%)	0.000
Sepsis	48 (76.1%)	44 (36.3%)	0.000
Necrotizing enterocolitis	12 (19.0%)	11 (9.0%)	0.053
Patent ductus arteriosus	28 (44.4%)	25 (20.6%)	0.001
PIVH	31 (49.2%)	20 (16.5%)	0.000
Bronchopulmonary dysplasia	35 (55.5%)	16 (13.2%)	0.000
Surfactant	34 (53.9%)	30 (24.8%)	0.000
Indomethacin	24 (38.1%)	22 (18.2%)	0.003
Corticoid	3 (4.8%)	3 (1.6%)	0.336
Central venous catheter	42 (66.7%)	34 (28.1%)	0.000
Mechanical ventilation (hours)	264 (24 - 1032)	120 (12 - 1296)	0.000

SGA: small for gestational age; RDS: respiratory distress syndrome; PIVH: peri-intraventricular hemorrhage.

**TABLE 2** Characteristics of parenteral and enteral nutrition.

Parenteral nutrition	Days to maximum supply		p
	Group 1 (n=63)	Group 2 (n=106)	
Glucose	5 (1 - 26)	4 (1 - 35)	0.283
Amino acids	7 (2 - 33)	6 (2 - 31)	0.106
Lipids	6 (2 - 31)	7 (2 - 38)	0.085
Initial glucose (g/kg/day)	5.8 (1.5 - 10.0)	7.3 (0.3 - 11.5)	0.000
Maximum glucose (g/kg/day)	9.8 (5.7 - 18.2)	13.3 (5.3 - 18.6)	0.000
Initial amino acid (g/kg/day)	0.5 (0.5 - 1.5)	1.0 (0.5 - 2.0)	0.002
Maximum amino acid (g/kg/day)	2.0 (0.5 - 3.5)	2.0 (0.5 - 4.0)	0.967
Initial lipid (g/kg/day)	0.5 (0.5 - 1.0)	0.5 (0.5 - 1.5)	0.001
Maximum lipid (g/kg/day)	2.0 (0.5 - 3.0)	2.0 (0.5 - 3.5)	0.746
Initial energy (kcal/kg/day)	24.9 (10.1 - 42.3)	34.7 (1.0 - 49.1)	0.000
Maximum energy (kcal/kg/day)	51.1 (27.3 - 87.1)	60.1 (27.2 - 96.2)	0.000
Start of PN (days)	2 (1 - 6)	3 (1 - 11)	0.472
Duration of PN (days)	11 (2 - 104)	8.5 (1 - 68)	0.006
Enteral Nutrition	Group 1 (n=63)	Group 2 (n=121)	p
Human milk (days)	13 (1 - 60)	7 (1 - 44)	0.004
Human milk and Formula (days)	14 (1 - 97)	9 (1 - 46)	0.002
Preterm formula (days)	27 (2 - 88)	24 (1 - 64)	0.107
Start of EN (days)	4 (1 - 16)	3 (1 - 11)	0.000
Duration of minimum EN (days)	2 (1 - 30)	1 (1 - 15)	0.000
Time for exclusive EN (days)	15 (3 - 42)	11 (5 - 69)	0.001
Duration of EN (days)	44 (1 - 95)	23.5 (7 - 76)	0.000
Time to 120 kcal/kg/day (days)	22 (10 - 52)	15 (7 - 63)	0.000

PN: parenteral nutrition; EN: enteral nutrition.

(20.6%), in G1, and 49 (46.2%), 35 (33.0%) and 22 (20.8%), in G2, both without statistically significant differences. The duration of PN was longer (p=0.006) in G1 compared to G2. There was a significant difference between the groups for most of the EN variables (Table 2). Seven children (11.1%) in G1 and 3 children in G2 (2.5%) did not receive human milk (p=0.002).

Most variables related to neonatal growth were different between the groups. The percentage of weight loss was greater (p=0.009) in G1 (13.4%; 0.4 to 44.7%) than in G2 (10.0%; 0.7 to 23.3%), the time to regain birth weight was longer (p=0.005) in G1 (17.7, 9.5 days) compared to G2 (12.9, 6.0 days) and the average daily gain was lower (p=0.000) in G1 (20.5, 0.8 g) compared to G2 (25.7, 2.5 g). The time to reach 1800 g was longer (p=0.000) in the extremely low birth weight at birth group (46 days; 9 to 81 *vs.* 21 days; 9 to 25). The frequency of SGA infants at post-conceptual age of term was higher in G1, 52 (82.5%) *vs.* 88 (72.7%), but without statistical significance (p=0.139).

To assess the factors associated with maximum weight loss greater than 10% of birth weight, time to regain birth weight greater than 14 days and frequency of SGA at post-conceptual age of term, the logistic regression model included gender, birth weight, SGA at birth, respiratory distress syndrome, sepsis, necrotizing enterocolitis, mechanical ventilation > 7 days, use of PN > 8 days, maximum glucose supply < 16.0 g/kg/day, maximum amino acid supply < 2.0 g/kg/day, maximum lipid < 2.0 g/kg/day and energy supply < 60 kcal/kg/day and time to achieve exclusive EN and energy supply of 120 kcal/kg/day by EN for more than 14 days. The results are presented in Table 3.

## DISCUSSION

With the increase in the survival of newborns with very low weight, reduction of morbidities and improved prognosis in the long term have become priorities. As such, neonatal nutrition is essential for adequate growth and development of preterm newborns.

According to recent recommendations, PN can be initiated within the first hours of life, and is safe and effective even in very premature infants.<sup>13-15</sup> In this study, PN was administered to 92% of newborns, but only 50% started it within the first 48 hours of life. Glucose administration was performed early, with an appropriate initial supply,<sup>16,17</sup> and although the duration of PN was sufficient, the maximum supply achieved was lower than recommended. The incidence of hyperglycemia is high in extremely premature infants and may limit the administration of glucose in these newborns.<sup>18</sup>

**TABLE 3** Final logistic regression model to assess the relationship between clinical and nutritional variables and growth variables.

	OR	95CI	p
<b>Weight loss &gt;10% of birth weight</b>			
Respiratory distress syndrome	3.024	[1.385; 6.605]	0.005
>14 days to 120 kcal/kg/day	3.442	[1.517; 7.719]	0.030
> 14 days to regain birth weight			
SGA	0.302	[0.127; 0.717]	0.007
Sepsis	2.636	[1.254; 5.540]	0.010
Maximum energy via PN <60 kcal/kg/day	3.029	[1.425; 6.442]	0.004
>14 days to 120 kcal/kg/day	4.551	[1.753; 11.814]	0.001
<b>Small for post-conceptual age of term</b>			
SGA at birth	9.995	[2.134; 46.826]	0.004
Sepsis	4.253	[1.496; 12.087]	0.006
>14 days for exclusive EN	6.994	[2.174; 22.501]	0.001

PN: parenteral nutrition; EN: enteral nutrition.

The infusion of glucose with amino acids on the first day of life decreases protein catabolism, increases protein incorporation rates, can help lower plasma glucose concentrations and should be started within the first days of life.<sup>17,19</sup> Studies comparing a high *versus* low supply of amino acids in the first days of life showed that high protein supplies resulted in increased protein incorporation without increasing toxicity,<sup>20-26</sup> with initial supplies of 3.0 g/kg/day being recommended. In our study, only 53% received amino acids in the first 48 hours of life, and the initial and maximum supplies were low, taking 6 to 7 days to reach the maximum supply. This practice exposed newborns to a negative protein balance and may have contributed to the low supply of glucose and energy.

Lipid emulsions are fundamental in PN for preterm newborns to meet the energy requirements for maintenance and growth and to prevent a deficiency of essential fatty acids. Lipid administration strategies include a minimum supply of 0.5 to 1.0 g/kg/day, starting on the first day of life, increasing 0.5 to 1.0 g/kg day to a maximum of 3.0 g/kg/day, attained in 4 to 5 days.<sup>15,16,27,28</sup> In this study, approximately 50% of patients received lipid emulsion after 48 hours of life, the initial and maximum doses were low and it took 6 to 7 days to reach the maximum dose. This lipid supply was sufficient to meet the essential fatty acid requirements, but contributed to the low supply of energy. This conservative approach may have been the result of concerns with toxicity. However, a me-

ta-analysis showed no differences between groups who received an early supply and those who did not receive an early supply of lipids in terms of growth, death and chronic lung disease outcomes.<sup>29</sup>

In the present study, EN was in line with the recommendations for best practices.<sup>30</sup> Minimum EN was started early, its duration was short and the progression to exclusive EN was quick. EN in newborns of very low birth weight is often delayed for several days or weeks after birth, due to cardiorespiratory complications and concern about necrotizing enterocolitis.<sup>31</sup> However, minimal enteral nutrition, especially human milk, provides numerous benefits and has been associated with a shorter time to reach exclusive EN, as well as reduced infection associated with central venous catheter, without increasing the incidence of necrotizing enterocolitis.<sup>32</sup>

The proposed increment of 20 mL/kg/day for EN is considered safe according to studies showing that increments of up to 30 mL/kg/day were not associated with increased incidence of necrotizing enterocolitis.<sup>33</sup> With the increase in volume adopted, the time to achieve exclusive enteral nutrition was appropriate.

The frequency of interruptions in EN was high (29.9%), but similar to those observed by Caple et al. of 26.8 and 29.6% for infants with low birth weight with increases in volume of 20 to 30 mL/kg/day, respectively.<sup>33</sup> The diagnosis of necrotizing enterocolitis was frequent in this study (12.5%). The use of human milk was common, especially among newborns of extremely low birth weight, and may be a protective factor for enterocolitis;<sup>34,35</sup> however, the mother's own milk or that from a donor was always pasteurized, which may have compromised its immunological capacity.<sup>36</sup> In addition to stimulating the use of raw human milk from the actual mother, we should pay attention to some aspects of routine EN. As observed by Henderson et al., a shorter duration of minimal enteral nutrition and greater speed for attaining exclusive EN may be modifiable risk factors for the development of necrotizing enterocolitis.<sup>37</sup>

On the other hand, the time to reach 120 kcal/kg/day was long and may be related to the high frequency of feeding interruptions and diagnosis of necrotizing enterocolitis. The delay in attaining this energy supply was associated with greater weight loss and longer time to regain birth weight.<sup>38</sup> The delay in regaining birth weight was also associated with low energy supply via PN, and the time to regain birth weight is a significant predictor of poor postnatal growth.<sup>39</sup> The low energy supply via PN and the delay in achieving the maximum recommended supply in this population may be markers of an accumu-

lated energy deficit and explain the higher percentage of weight loss and slower weight gain.<sup>40,41</sup>

Logistic regression analysis also showed that respiratory distress syndrome is associated with increased weight loss, which may be secondary to an inadequate supply of nutrients; this is especially difficult in children with respiratory failure.<sup>42</sup> Sepsis increased the risk of delayed recovery of birth weight, and has been associated with slower weight gain during hospitalization;<sup>43</sup> newborns with sepsis may develop intolerance to glucose and lipids, limiting the supply of these nutrients. As described by other researchers,<sup>43,44</sup> SGA infants recovered their birth weight earlier. In this study, the SGA preterm infants had a greater gestational age than those of suitable weight for age (27.7 *vs.* 30.6 weeks) and may have presented a lower frequency of conditions that interfere with nutritional therapy.

The restriction of intrauterine growth is extremely common in children with very low birth weight.<sup>6,14,44,45</sup> In our population, the frequency of newborns with weight below the 10<sup>th</sup> percentile for age increased from 30.4% at birth to 76.1% at post-conceptual age of term, and the associated factors were SGA, sepsis and higher time for attaining exclusive enteral nutrition. The association between restriction of extra-uterine growth, SGA, bronchopulmonary dysplasia, number of days of parenteral nutrition and age to attain exclusive enteral nutrition has also been shown in other studies.<sup>6, 40-42</sup>

Nutritional practices for preterm infants vary considerably between NICU and there is no definite strategy with proven capacity to safely optimize nutrition, growth and development.<sup>10</sup> However, the implementation of a program with potentially better nutritional practices can promote a more adequate supply of nutrients and stimulate growth.<sup>9</sup>

## RESUMO

Práticas nutricionais e restrição de crescimento pós-natal em prematuros

**Objetivo:** avaliar as práticas nutricionais em unidade de cuidados intensivos neonatais (UCIN) associadas a déficit de crescimento em recém-nascidos pré-termo (RNPT). **Métodos:** estudo retrospectivo de RNPT com peso entre 500 e 1.499 g internados em UCIN. Analisaram-se: evolução do crescimento e práticas de nutrição parenteral (NP) e enteral (NE).

**Resultados:** dentre 184 RNPT divididos em G1 (500 a 990 g; n=63) e G2 (1.000 a 1.499 g; n=121), 169 receberam NP (G1=63; G2=106). Comparando-se com as reco-

mendações, a NP foi iniciada tardiamente, sua progressão foi lenta e as ofertas máximas de glicose, aminoácidos, lipídios e energia foram baixas nos dois grupos. A oferta inicial de aminoácido e lipídio e a inicial e máxima de glicose e energia foram menores no G1. O início da NE foi precoce (1 a 2 dias), o tempo para atingir NE exclusiva foi adequado (11 a 15 dias), e o uso de leite humano foi possível por tempo razoável (7 a 13 dias). A análise multivariada mostrou que a síndrome do desconforto respiratório e o alcance tardio da oferta de 120 kcal/kg/dia aumentaram a chance de perda de peso superior a 10%. Sepse, oferta energética máxima por NP < 60 kcal/kg/dia e alcance tardio da oferta de 120 kcal/kg/dia aumentaram a chance de recuperar o peso de nascimento após 14 dias, enquanto a condição de pequeno para idade gestacional (PIG) ao nascimento reduziu essa chance. PIG ao nascimento, seps e alcance de NE exclusiva após 14 dias aumentaram a chance de ser PIG na idade pós-conceitual de termo.

**Conclusão:** aprimorar as práticas nutricionais em UCIN pode reduzir o déficit de crescimento em prematuros de muito baixo peso ao nascer.

**Palavras-chave:** prematuro, nutrição enteral, nutrição parenteral, recém-nascido de muito baixo peso.

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