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# Aggressive parenteral nutrition and growth velocity in preterm infants

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**Abstract**

***Introduction:*** **Parenteral administration of nutrients to sustain newborns' growth represents an important therapeutic challenge.**

***Objective:*** **To describe parenteral nutrition (PN) practices in a tertiary hospital and evaluate postnatal growth in preterm infants.**

***Material and methods:*** **Observational retrospective study over 3 months. Data on infants born or admitted to the Neonatal Department and starting PN were collected. Demographics, anthropometric data, daily caloric, protein intake data and PN components used were collected. Growth velocity was characterized by the average daily weight gain and compared to intrauterine growth.**

***Results:*** **68 preterm infants started PN during the study period. Most infants (65%) were born by caesarean and mean gestational age was 33 weeks. Twenty five percent of newborns did not regain birth weight. The remaining 75% regained birth weight on the 3rd day of PN and average daily weight gain was 16 g/kg/d, ranging between 12 and 22 g/kg/d. Although weight gain approximated intrauterine rate, most infants born <30 weeks gestation did not achieve median birth weight of the reference population. Early aggressive PN was administered with an average of 3, 11 and 3 g/Kg/d of proteins, carbohydrates and lipids respectively, reaching a maximum on the 4th day of 4, 18, 4 g/kg/d, respectively.**

***Discussion:*** **Aggressive PN is used in the hospital setting. The preterm infants reached birth weight earlier and had a greater velocity of growth than in other clinical trials and similar to intrauterine.**

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Key words: *Parenteral nutrition*. *Preterm infants*. *Growth*.

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**NUTRICIÓN PARENTERAL INTENSIVA Y VELOCIDAD DE CRECIMIENTO EN RECIÉN NACIDOS PREMATUROS**

**Resumen**

***Introducción:*** **La administración parenteral de nutrientes para mantener el crecimiento en recién nacidos representa un importante reto terapéutico.**

***Objetivo:*** **Describir las prácticas de nutrición parenteral (NP) en un hospital de tercer nivel y evaluar el crecimiento postnatal en recién nacidos prematuros.**

***Material y métodos:*** **Estudio observacional retrospectivo de 3 meses de duración. Se incluyeron niños ingresados en el Servicio de Neonatología que iniciaron NP. Se recogieron datos demográficos, antropométricos, calorías diarias, ingesta de proteínas y componentes de la NP. La velocidad de crecimiento se midió mediante la media de la ganancia diaria de peso y se comparó con el crecimiento intrauterino.**

***Resultados:*** **68 niños prematuros iniciaron NP durante el período de estudio. La mayoría de los niños (65%) nacieron por cesárea y la media de edad gestacional fue de 33 semanas. El 25% de los recién nacidos no recuperó el peso de nacimiento. El 75% restante recuperó el peso de nacimiento en el tercer día de NP y la media de la ganancia diaria de peso fue de 16 g/kg/d, con un rango de 12 a 22 g/kg/d. A pesar de que la ganancia de peso se acercó a la tasa intrauterina, la mayoría de los niños nacidos con menos de 30 semanas de gestación no lograron la media de la población de referencia. La NP precoz e intensiva se administró con una media de 3, 11 y 3 g/Kg/d de proteínas, hidratos de carbono y lípidos, respectivamente, alcanzando un máximo en el cuarto día de 4, 18, 4 g/kg/d, respectivamente.**

***Discusión:*** **La NP intensiva se utiliza en el ámbito hospitalario. Los recién nacidos prematuros alcanzaron antes el peso de nacimiento y presentaron una velocidad de crecimiento mayor que en otros estudios y similar al crecimiento intrauterino.**

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Palabras clave: *Nutrición parenteral*. *Pretérmino*. *Crecimiento*.

## Abbreviations

ELBW: Extremely low body weight.
ESPEN: European Society for Clinical Nutrition and Metabolism.
HC: head circumference.
LBW: low body weight.
PI: preterm infant.
PN: parenteral nutrition.

## Introduction

There is an increasing rate of prematurity in developed countries due to the use of assisted reproductive technology. The advances in perinatal care allow neonatal survival of increasingly immature infants[1]. According to the Spanish National Statistics Institute, prematurity rates vary between 6 and 7%, 1 to 2% are infants with a gestational age below 32 weeks and about 1% newborns weighing less than 1,500 g[2].

Newborn infants differ from adults in that their food intake must provide sufficient nutrients not only for maintenance of body tissues but also for growth. Based on body weight, the energy and nutrient requirements of newborns are higher than in older patients. A preterm infant (PI) has an extremely low body store of nutrients and sufficient reserve to survive only four days of starvation[3]. The gastrointestinal tract, muscular and neurological immaturity and necrotising enterocolitis are a variety of reasons for premature infants requiring immediate parenteral nutrition (PN). Moreover, premature infants born early in the third trimester of pregnancy suffer growth restriction due to lack of supply of intrauterine nutrients[4-6]. The ability to provide sufficient nutrients parenterally to sustain growth in infants, especially less than 32 weeks gestational age infants, represents a challenge and one of the important therapeutic advances in paediatrics over the last three decades[3].

The history of neonatal feeding practices has undergone many modifications. Following the past nutritional recommendations, such as total fasting, little growth observed[7]. Current scientific evidence highlights the importance of supplementing the premature infant with sufficient nutrients not only to improve survival, growth and neurological development, but also to secure future health and quality of life[8-10].

In 1948, Dancis et al published growth curves derived from 100 preterm infants with birth weights ranging from 1,000 to 2,500 g[11]. Those curves are still widely used today, despite major changes in many aspects of neonatal care, including nutritional support. More recent trials have described postnatal weight changes in surviving PI and the growth rates for low body weight (LBW) infants exceeding those predicted by Dancis curves[12-17]. The American Academy of Paediatrics Committee on Nutrition goal is to provide nutrient intake permitting "a rate of postnatal growth and the composition of weight gain to approximate that of a normal foetus of the same postnatal age". Achievement of postnatal growth at a rate approximating that of the third trimester of intrauterine life is considered the best means of facilitating later growth and development with the aid of growth charts and child growth assessment[18,19].

## Objectives

The primary objective was to describe postnatal weight gain in response to current nutrition practice in different birth weight infants receiving PN in a hospital setting and to observe if intrauterine growth was achieved. Secondary objectives were to describe current nutritional practices, determine if the established protocol created by the Neonatal and Pharmacy Department is followed and compare them to the American Academy of Paediatrics Committee recommendations.

## Material and methods

We performed a retrospective cohort study. Data were collected on infants born in or admitted to the Neonatal Department and starting parenteral nutrition between december 2011 and february 2012. PI with PN lasting less than 3 days were excluded from the study. Data for each eligible infant were retrospectively collected: gender, birth, gestational age, hospitalization diagnosis, days with PN, PN start day, daily weight, length and head circumference from the regime period, blood levels of sodium, potassium, chloride, calcium, glucose, bilirrubin, haemoglobin during PN, PN composition (proteins, lipids and carbohydrates) on the 1st and 4th day and maximum rate, the quality of the components used in the PN preparation and use of a standard starter solution. Gestational age was based on best obstetrical estimation; weight was performed by nurses as routine clinical practice with digital electronic scales (reading to at least the nearest 10g). Head circumference was determined by applying a paper measurement tape firmly around the head above the supraorbital ridges and over the part of the occipital that gave the maximum circumference. Recumbent length was measured with paper measurement tape. The starter solution contained 52.5ml comprised of 1.5g of amino acids and 3.75g of glucose, with a total calorie input of 21kcal, prepared twice weekly at the Pharmacy Department following the European Society for Clinical Nutrition and Metabolism (ESPEN) recommendations and stored in the Neonatal Department. This was used whenever a newborn could not receive individualized parenteral nutrition in the first hours of life, therefore mainly in births in the evenings and weekends. PN is prepared with Primene® containing in 1L 100g of amino acids, taurine 0.6g, tyrosine 0.45 g and cysteine 1.89 g, clinoleic 20% as a lipid emulsion and glucose at different concentrations to adjust the volume required in every patient.

Daily caloric and protein intake data were based on pharmacy prescriptions and collected from the parenteral nutrition compounding program (Medical One Parenteral®) used at the Pharmacy Department to prepare PN. Demographics and serial anthropometric data were collected from the electronic and paper clinical record. In the statistical analysis, for each variable: the mean, standard deviation and range was obtained using Excel® and SPSS (vs. 15).

Excepting the starter solution, individualized PN was prescribed daily by neonatologists depending on infant metabolic picture and medical criteria, validated by pharmacists and prepared by nurses at the Pharmacy Department following good manufacturing practices. PN composition was compared with the American Academy of Paediatrics Committee recommendations and the existing protocol in the Neonatal unit as to its content of glucose, amino acids and lipids[20].

Due to the heterogeneity in pathophysiology and the differing maturity of patients, it was necessary to classify preterm infants according to birth weight, stratified by 1000g birth weight intervals: >2,000 g, 2,000-1,000 g and <1000 g (Extremely low body weight, ELBW).

The average daily increments for body weight (g/d and g/kg/d) characterized the velocity of growth and were computed for the period between the parenteral nutrition start and end and compared to intrauterine growth normal rate. To assess preterm infants' postnatal growth, a growth curve was developed. To show the trend in the change of weight, 30 days on PN are shown assuming the last days are represented by fewer infants. Finally, growth velocity was compared with data reported by NICHD Growth Observational Study population[21]. The average increment for length in this period was also reported.

The study was approved by the Hospital Ethics Committee.

## Results

Sixty eight preterm infants started PN during the study period. Characteristics of the entire study population stratified by 1000g birth weight intervals are displayed in table I. The majority of infants (65%) were born by caesarean. Seventy percent of principal hospitalization diagnosis was prematurity which explains the use of PN. Mean gestational age was 33 weeks.

Anthropometric measurements during the study period and the infants' velocity of growth are displayed in table II. Seventy five percent of patients regained birth weight on the 3rd day of PN and the average daily weight gain was 16 g/kg/d, variable across 1,000 g-birth weight intervals, ranging between 12 and 22 g/kg/d. According to The American Academy of Paediatrics, normal intrauterine growth rate is 15 g/kg/day[20], therefore, intrauterine growth was achieved in newborns with <1,000 g and >2,000 g birth weight. Curves plotting growth velocity versus days on PN for each 1000g birth weight stratum in this population are shown in figure 1. Growth in length averaged 0.9 cm/week and 0.2 cm/week in Head Circumference

**Table I**
*Nutritional and demographic characteristics*

| | *Gestational age (weeks) (SD)* | *Caesarean Born* | *Gender (% male)* | *Principal hospitalization diagnosis* | *Days in PN (SD)* | *Day neonates regained birth weight (SD)* |
|---|---|---|---|---|---|---|
| <1000 g (n = 14) | 26 (2.1) | 72% | 50% | Prematurity (83%) | 48 (24) | 4.3 (4.0) |
| 1000-2000 g (n = 30) | 31 (2.6) | 67% | 47% | Prematurity (80%) | 13 (13) | 5.5 (6.1) |
| >2000 g (n = 24) | 37 (2.3) | 58% | 33% | Congenital heart disease (29%) | 14 (17) | 0 |
| TOTAL (n = 68) | 33 (4.9) | 65% | 43% | Prematurity (67%) | 20 (22) | 3.3 (7.2) |

SD: standard deviation.

**Table II**
*Anthropometric characteristics before and after PN and velocity of growth*

| | *Before PN* | | | *After PN* | | | *Velocity of growth* | | |
|---|---|---|---|---|---|---|---|---|---|
| | *Length cm (SD)* | *Weight g (SD)* | *HC cm (SD)* | *Length cm (SD)* | *Weight g (SD)* | *HC cm (SD)* | *Length gain (cm/wk)* | *Weight gain (g/kg/d)* | *HC gain (cm/wk)* |
| <1000 g (n = 14) | 33 (3.5) | 810 (117) | 23 (1.4) | 42 (7.5) | 1419 (327) | 26 (5.0) | 1.4 | 15 | 0.4 |
| 1000-2000 g (n = 30) | 41 (3.9) | 1545 (338) | 29 (1.9) | 42 (2.7) | 1653 (305) | 29 (2.0) | 0.6 | 12 | – |
| >2000 g (n = 24) | 49 (3.0) | 3071 (529) | 34 (1.4) | 51 (3.8) | 3356 (701) | 35 (1.0) | 1.0 | 22 | 0.5 |
| TOTAL | 43 (6.8) | 1932 (971) | 30 (4.6) | 45 (5.4) | 2249(815) | 30 (4.1) | | | |

SD: standard deviation
PN: Parenteral Nutrition
HC : Head Circumference

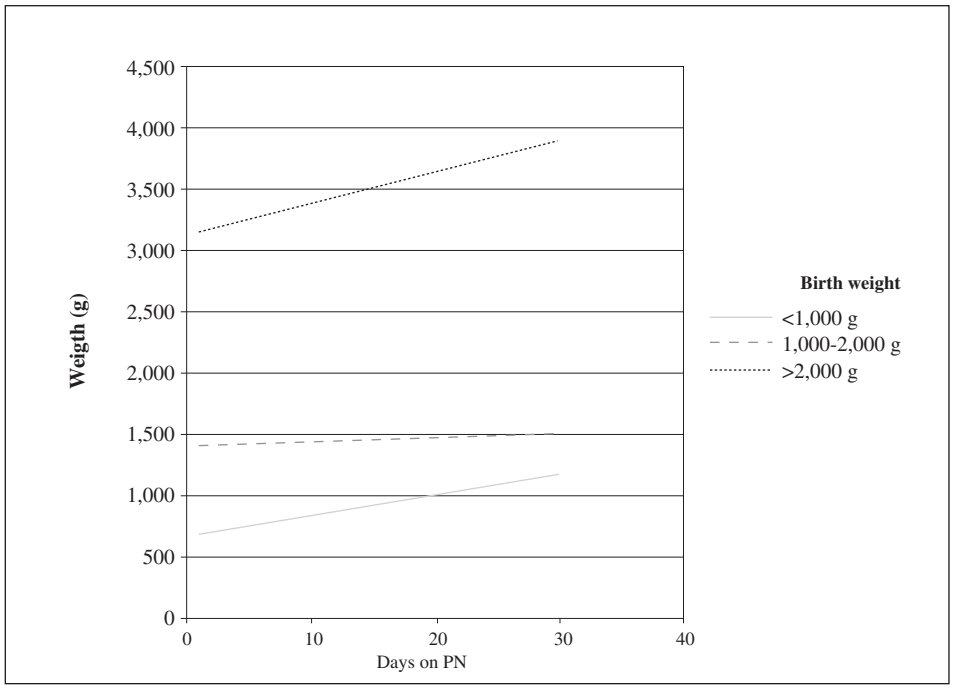


*Fig. 1.—Weight change stratified by birth weight.*

(HC). Using Rho Spearman nonparametric correlations, positive correlations between weight, height and length were demonstrated at the start and end of the study, indicating that infants who tended to fast ?growth in one measure also tended to fast growth in the others. Unlike NICHD infants, neonates weighing more than 2000g did not experience the initial weight loss after birth, neonates from 1000 to 2000g regained birth weight earlier. Finally, ELBW neonates also regained the birth weight faster and had a higher growth rate[21].

PN composition on the 1st, 4th day and maximum dosages are described in table III as well as the hospital protocol and the American Academy of Paediatrics Committee's recommendations. The established neonatal protocol is generally well followed at the hospital as can be deduced from the nutrition contributions described on day 1, 4 and the average maximun rate used. The upper limit dose of nutrients currently used exceeded the established protocol of every nutrient as well as the American recommendations concerning glucose dosage. Average individualized PN start day was the first day after birth. All PI less than 2,000 g started PN in the first hours of life, at overall rates of 2.4 and 1.3 g/kg/d of proteins and lipids. Sixty eight percent used the starter solution prepared at the Pharmacy Department at a rate of 2 solutions per kg per day (105 ml, 3 g and 7.5 g/kg/d of volume, aminoacids and glucose respectively) and an average duration of 1.6 days. Eighty five percent of infants weighing more than 2,000 g started PN before the first 48 hours of life.

Blood levels were on range before and after PN with a significant decrease in glucose from 113 to 87.5 mg/dl and haemoglobin from 16.4 to 14.4 g/dl.

## Discussion

The increasing survival of low birth weight infants is still currently a challenge for the full medical team. As reported by Dancis et al "the chief variable in determining the weight curve of a premature infant is the feeding policy"[11]. The clinical interpretation of growth

**Table III**
*Daily intakes and nutrients' recommendations*

| | *1st day (SD)* | *4th day (SD)* | *Maximum (SD)* | *Upper Limit* | *Established hospital protocol* | *American Academy of Paediatrics Committee recommendations*[20] |
|---|---|---|---|---|---|---|
| Aminoacids g/kg/d | 2.4 (0.5) | 2.8 (1.0) | 3 (0.8) | 4 | 2.5-3.5 | 2-4 |
| Glucose g/kg/d | 7.8 (4.3) | 9.2 (10.1) | 10.9 (10.6) | 18 | 6-12 | 4-16 |
| Lipids g/kg/d | 1.3 (1.0) | 2.2 (1.5) | 2.7 (1.4) | 4 | 0.5-3 | 3-4 |

SD: standard deviation

rate for individual infants is hindered by multiple factors and the marked changes in prenatal medicine during the past 5 to 10 years. We therefore chose to evaluate a heterogeneous population of hospitalized preterm infants in an effort to determine postnatal growth in response to current nutritional practices and as a first step to improve postnatal growth and nutritional status.

Aggressive nutrition, defined by studies is the use of high nutrient dosages, starting in the first hours of life[18,22]. PN prepared by the Pharmacy Department is comprised within aggressive nutrition as newborns are fed with an average of 3, 11 and 3 g/kg/d of proteins, carbohydrates and lipids respectively, following the established protocol and exceeding it occasionally at a maximum rate of 4, 18 and 4 g/kg/d respectively.

The amount and quality of protein intake influence newborn metabolism and growth and contribute to minimizing protein catabolism and to promoting protein synthesis. Twenty six percent of infants in the study received 4 g/kg/d of protein exceeding the established protocol but not the American recommendations. A metanalysis of PI <2,500 g showed that children with a protein intake between 3 and 4 g/kg/d had a greater weight gain and nitrogen retention compared to those with lower intake[23,24]. Proteins are supplied as aminoacids solution and must contain an adequate proportion of essential and nonessential aminoacids. Cysteine due to its antioxidant properties and tyrosine and taurine which improve neonatal cholestasis and prevent retinal alteration are essential aminoacids in preterm infants and are included in the parenteral solutions prepared at the hospital[3,25]. Brain development and function rely heavily on lipids. Due to liver immaturity and decreased bile acid synthesis during the first weeks of life, lipids are recommended to be started on the 1st or 2nd life day and raised to 2 to 2.5 g/kg/d. Mean lipid rate in the study was 2.7 g/kg/d with a maximum of 4g/kg/d, at the upper limit of American recommendations and higher than the protocol. Lipid emulsions are used at 20%, as it would seem that this prevents lipid peroxidation, providing a higher antioxidant intake and having immunological advantages with respect to fat emulsions based on soybean oil[26]. Regarding glucose maximum rates and doses within the first 24 hours of life, randomized controlled trial evidence is still limited. Although some studies have used 20 g/kg/d, ESPGHAN guidelines do not recommend rates higher than 18 g/kg/d[9].

Recent studies support the importance not only of the amount and quality but also of a fast achieval of maximum nutrient levels[8]. Early administration of proteins decreases the frequency and severity of neonatal hyperglycemias by stimulating endogenous insulin secretion and promotes growth by stimulating the Insulin-Growth Factors. Thureen et al studied the efficacy and safety of a more aggressive aminoacid intake of 3 g/kg/d versus 1 g/kg/d beginning at about 24 hours of age[27]. Protein balance was significantly higher with no evidence of toxicity. Kotsopoulos et al evaluated the initiation of 1.5 g protein/kg/d at less than 6 hours age[28]. The infants regained weight faster and had a lower incidence of late-onset sepsis. Ibrahin et al described the advantages of early aggressive parenteral nutrition in which not only proteins but also lipids were initiated within 2 hours of birth at a rate of 3g lipid/kg/d[29]. Nitrogen balance and energy intake increased without increasing the risk of metabolic acidosis. In the study, all <2,000 g weight birth infants started PN in the first 24 hours of life, which also demonstrates a high efficiency and coordination between physicians and pharmacists. The introduction of the starter solution by the Pharmacy Department has been a major improvement in reducing time in initiation of PN providing glucose and amino acids.

However in the study conducted by Gomis et al, the percentage of patients who received PN the first day of life was only 30% in patients born on weekdays, due in part to the lack of availability of PN during afternoon and night shifts as individualized PN was only prepared on weekdays in the morning[30].

On the 4th day of nutrition, most infants were at maximum doses of every nutrient. Regarding PN duration, days differed significantly from ELBW and the rest of infants probably due to their critical clinical situation. The use of aggressive PN produces a more rapid growth and the curves are a reflection of changes in hospital nutritional management[31-34]. Our preterm infants have a better growth profile than those described in literature[12-17].

The average daily weight gain ranged around 16 g/kg/d, a rate similar to the reported intrauterine weight gain of 15 g/kg/d and higher to the ones described by Ehrenkranz et al, Wrigh et al and Shaffer et al[13,14,17]. In addition, the average weekly increment in length (0.9 cm) was also similar to intrauterine (1.1 cm/wk)[33]. Although weight gain approximates the intrauterine rate, most infants born < 30 weeks gestation would not have achieved the median birth weight of the reference foetus of the same postmenstrual age, and many would be near the 10 percentile at the start and end of PN. Intrauterine growth goal may be achievable for late preterm infants, but is usually difficult, and rarely met for <30 week gestation neonates. Even if there is debate on this target, it seems necessary because growth retardation could be a risk for long-term neurological development[10]. In fact, delays in regaining birth weight and low nutrient intakes play a mayor role in growth failure. The variability on the average daily weight gain across 1,000 g-birth weight intervals, can be explained due to the higher relative increase of ELBW infants as well as to the great diversity in the highest birth weight group.

On one hand, this study may be helpful as it is based on current nutritional practices and can be used to better understand postnatal growth and improve nutritional daily practice resulting consequently in a more rapid weight gain and hopefully short and long-term

outcomes. Steps to ensure adequate nutritional support have been taken: maximum protocolized doses have been increased and fixed at a rate of 4, 16 and 4 g/kg/d of proteins, carbohydrates and lipids respectively. Results have been shown to physicians to encourage the use of early aggressive parenteral nutrition and ensure newborn weight is registered every day. Finally, the growth curves and nutritional data may be useful in identifying slow growth PI despite current nutritional support and in designing individualized nutritional interventions. On the other hand, this study has collected data on ELBW infants, useful as there is surprisingly little evidence-based data and questions as optimum time to begin aminoacid and lipid supply, remain with regard to such infants[35].

No exclusion criteria were selected as we wanted to evaluate parenteral nutrition use and neonates' growth in clinical practice. One limitation of the study is that neither disease as congenital heart failure or inborn/congenital? errors of metabolism, nor neonate co-morbidity were collected which could change the needs of nutrients and their proportion. Therefore, slower growth could result from "suboptimal nutritional support" provided or due to the existence of morbidities. Moreover, conclusions drawn are also limited by the fact that data were collected retrospectively and birth weight was not registered daily for all newborns. Long-term outcomes were not specified and neither the metabolic complications from the use of aggressive PN that affect the ability to meet the nutrients' requirements. Finally, timing of initiation and speed of advancement of enteral feedings were not registered. Therefore growth could also result from enteral nutrition.

In summary, even if ELBW infants did not achieve the median birth weight of a reference foetus of the same postmenstrual age, preterm infants have a greater growth velocity and reach birth weight earlier than in other clinical trials and similar to intrauterine, probably due to early aggressive PN and excellent cooperation between neonatologists, pharmacists and nurses. The early aggressive PN used at the hospital ensures that the transition from the intrauterine to the extrauterine environment occurs with minimal disruption.

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