Growth and Neurodevelopment in Preterm Infants Receiving Early, Intensive, Enteral and Parenteral Nutritional Support.

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Abstract

Title: Growth and Neurodevelopment in Preterm Infants Receiving Early, Intensive, Enteral and Parenteral Nutritional Support.
Background: CNS indemnity, which is the result of intrinsic (genetic and hormonal) and extrinsic factors (nutrition, environment, social and emotional status), is indirectly measured by neurodevelopment assessment.
Objective: To evaluate growth, in comparison with a historical control group, at 40 weeks of corrected gestational age (cGA) and psychomotor development (PD) at one year of cGA in VLBW after nutritional intervention.
Design/Methods: Clinical trial with a historical control group. Population: inborn infants <32 weeks of gestational age and birth weight 750 and 1.500 g. Methods: in the treated group (TG) enteral and parenteral nutrition were started on the first day of life. The control group (CG) was fed in accordance with the opinion of the attending physician, resulting in a higher cumulative energy and protein deficit at the end of the fourth week of life (794 Kcal in CG vs 353 in TG and 34 g vs 11 respectively, p<.001). Main endpoints: undernutrition (body weight <10th percentile at 40 cGA weeks), and PD through Rodriguez and col. scale. PD was analyzed using a multivariate model that included as covariates: prenatal steroids, small for gestational age, grouped neonatal morbidity, and maternal education level.
Results: 101 patients completed the evaluation at one year of cGA, 65 in the TG and 36 in the CG. Birth weight (1150 vs. 1190 g), gestational age (30 vs. 29 weeks), head circumference (HC) (25.9 vs 26.5 cm), small for dates (8% vs. 3%), and exposure to prenatal steroids (63% vs.75%) were similar in both groups. No difference was found in postnatal morbidity or in social, economic, or cultural status. Undernutrition at 40 weeks of cGA was lower in the TG (38% vs. 72%, p=.002). HC was larger in the TG (35.4 vs. 34.6 cm, p=.028). Univariate analyses showed PD was 0.13 higher in the TG (1.02 vs. 0.89, 95% CI: 0.049-0.224). This effect persisted in multivariate analyses, with PD increasing by 0.094 (95% CI: 0.012-0.175) in the TG. Maternal education was a significant variable for improving the PD by 0.014 (95% CI: 0.0003-0.0283).
Conclusions: In this population, patients who received early and intensive nutritional intervention had a lower frequency of postnatal undernourishment at 40 weeks cGA and better PD at one year of life.

Background

CNS indemnity, which is the result of intrinsic (genetic and hormonal) and extrinsic factors (nutrition, environment, social and emotional status), is indirectly measured by assessing neurodevelopment.
Low birth weight in preterm infants indicates a higher probability of postnatal growth failure (PGF), learning disabilities, and/or behavioral problems and can presage several adverse long term effects.
AGA preterm infants suffering PGF during the first weeks of life could be exposed to the same risks as those who are born small for gestational age. Inadequate nutrition during a vulnerable stage in the development of the CNS can permanently affect an infant´s brain size, neuron count, learning ability, and memory.
Nutritional intervention during the first weeks of life could minimize the nutritional deficit that takes place after birth and thereby reduce the potential for stunted growth and its harmful effects on neurodevelopment.
We showed in a previous study (1) that early and intensive nutritional intervention reduced postnatal undernourishment without any increase in morbidity, but did not prevent it completely. The most significant effects observed were a decrease in malnutrition at 40 weeks after conception, a higher rate of growth of the cephalic circumference, and a reduction in energy and protein deficits.

Objective

To evaluate growth, in comparison with a historical control group, in VLBW after early and intensive nutritional intervention at 40 weeks of corrected gestational age (cGA), and to evaluate psychomotor development (PD) at one year of cGA.

Design/Methods

Clinical trial with a historical control group. Population: inborn infants <32 weeks of gestational age and birth weight 750 and 1.500 g. Exclusion criteria were major congenital malformations and confirmed IU infection. Infants who died or were lost in the follow up were eliminated from the analysis.

Methods: in the treated group (TG) enteral and parenteral nutrition were started on the first day of life following the guidelines of the Nutrition Committee of the American Academy of Pediatrics (2) for energy and protein intakes, while in the historical control group (CG) patients were fed in accordance with the opinion of the attending physician.

Enteral Feeding: Early gastrointestinal tract maturation was enhanced with calostrum or premature formula (10 ml/k/d) from the first day of life and administered by gavage through an orogastric tube.
Day 1: Human milk or preterm formula 10 ml/kg/day.
Day 2 to 7: Increase in 10 ml/kg/day.
From day 8: Increase in 20 ml/kg/day, up to a maximum of 180 ml/kg/day.

Up to 100 ml/kg/d	**50% Human milk** **50% Premature Formula 24 Kcal/oz**
Up to 150 ml/kg/d	**1/3 Human milk** **2/3 Premature Formula 24 Kcal/oz**
From day 30	**1/4 Human milk** **3/4 Premature Formula 24 Kcal/oz**

Parenteral Nutrition:
From day 1, amino acids (Aminosteril® infantil 10% solution) were infused at 1,5 g/k/d. This was increased by 0.5 g/k/d to a maximum of 4 g/k/d.
Lipids were started using 20% MCT/LCT solution on the 2nd day at 0.5 g/k/d. This was increased by 0,5 g/k/d to 3,5 g/k/d and maintained in accordance with plasmatic trigliceride and cholesterol levels.
Parenteral nutrition was discontinued when 100 Kcal/k/d were reached enterally. At 36 weeks of postconceptional age, patients were fed ad libitum with human milk and/or premature formula.

Neurodevelopmental Evaluation:
At one year of cGA infants were tested using The Psychomotor Development Scale of Evaluation (EEDP) of Rodríguez et al (3), that includes 75 items involving the four areas of development: speech, motor, social and coordination, up to 2 years of age, establishing a Development Quotient (DQ). Patients were classified as normal (DQ > 0.84), at risk (DQ 0.7 to 0.84) or abnormal (DQ < 0.7).

Growth Evaluation:
Body weight was registered daily up to 28 days and then weekly up to 40 weeks of cGA using the Intrauterine Growth Charts from Maternidad Sardá (4). Length (L) and Head Circumference (HC) were registered at birth and then weekly until 40 weeks after conception.

Statistical Analysis:
Categorical variables were analyzed with the Chi Square test. Numerical variables were analyzed using parametric or non parametric tests in accordance with the data distribution. PD was analyzed using the multivariate model that included the following as covariates: prenatal steroids, smaller than average size for gestational age, neonatal morbidity, and the mother`s level of education.

Ethical Considerations:
The study was authorized by both, The Ethics and Research Committee of Materno Infantil "Ramón Sardá" Hospital.

Results

Between August 2001 and July 2003, 92 patients were born that met the inclusion criteria (treated group). 10 of these patients died, 3 were transferred before 40 weeks of age, and 14 dropped out of the follow-up. 52 preterm babies born in the previous year were included in the control group using the same criteria.
2 of these died, 8 were transferred, and 6 dropped out of the follow-up.
101 patients completed the evaluation at one year of cGA, 65 in the TG and 36 in the CG. Birth weights (1150 vs. 1190 g), gestational ages (30 vs. 29 weeks), head circumferences (HC) (25.9 vs 26.5 cm), the rates of small size for age (8% vs. 3%), and exposure to prenatal steroids (63% vs.75%) were similar in both groups. No difference was found in postnatal morbidity or in social, economic, or cultural status.

Table 1 Study Population

	Treated n= 65	Control n=36	p
MEAN GESTATIONAL AGE IN WEEKS (range)	30(26-31)	29(24-31)	ns
MEAN BIRTH WEIGHT (range)	1150 (750-1500)	1190 (750-1500)	ns
MALE GENDER n (%)	35 (55.38)	24 (66.67)	ns
MULTIPLE BIRTH n (%)	10 (15.38)	4 (11.11)	ns
MEAN YEARS OF MATERNAL EDUCATION (range)	9 (4-16)	8 (5-15)	ns

Table 2 Clinical Characteristics.

	Treated n= 65	Control n=36	p
IUGR (<pc10) n (%)	5 (7.69)	1 (2.78)	ns
ANTENATAL STEROIDS (≥1 course) n (%)	52 (80)	31 (86)	ns
DAYS MECHANICAL VENTILATION median (range)	5 (0-68)	5 (0-95)	ns
SURFACTANT THERAPY n (%)	35 (53.85)	18 (50)	ns
O2 AT 36 WEEKS n (%)	21 (32.3)	13 (36.1)	ns
PDA n (%)	39 (60)	19 (52.78)	ns
SEVERE IVH (G III - IV) n (%)	5 (7.69)	5 (13.89)	ns
PVL n (%)	6 (9.2)	5 (13.9)	ns
LATE ONSET SEPSIS n (%)	16 (24.6)	12 (33.3)	ns
ANY KIND OF MORBIDITY (IVH, BPD, ROP) n (%)	33 (50.77)	18 (50)	ns
NEC n (%)	1 (1.54)	2 (5.56)	ns
ROP (G III- IV) n (%)	7 (10.77)	8 (22.22)	ns

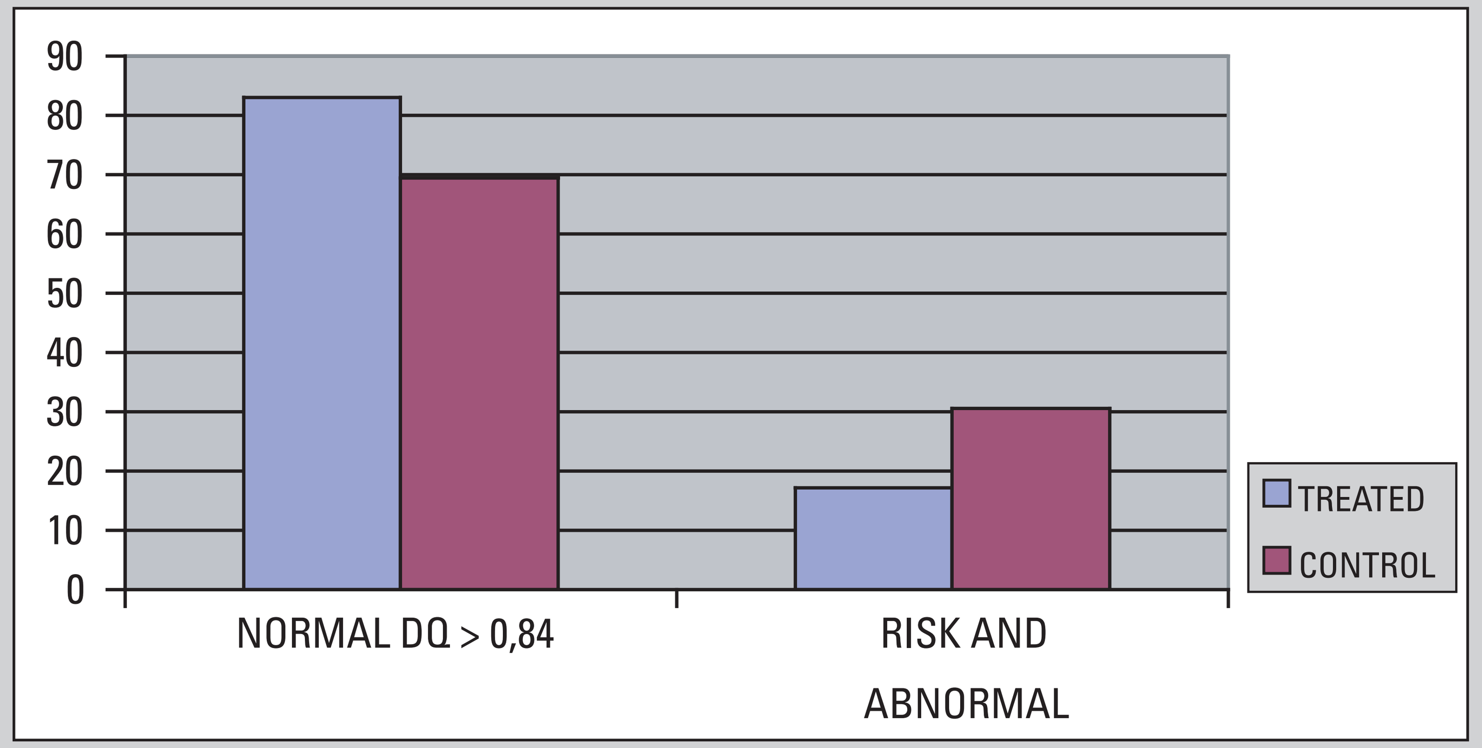
PDA: patent ductus arterioso; NEC: necrotizing enterocolitis; HIV: intraventricular hemorrhage; PVL: periventricular leucomalasia; ROP: retinopathy of prematurity.

Table 3 Nutritional Outcome

	Treated n= 65	Control n=36	p
Cumulative Energy Deficit at 28 days. Kcal Median (range)	-352 (-1358/221)	-793 (-1871/-155)	<.001
Cumulative Protein Deficit at 28 days in g Median (range)	-10.7 (-46/16)	-33 (-1/-14)	<.001
Mean Weight in g at 40 weeks (SD)	3170 (556)	2790 (352)	<.001
Length at 40 weeks in cm	47.3 (2.4)	46 (0.35)	NS
HC at 40 weeks in cm	35.4 (1.8)	34.6 (1.6)	.028
Gain in HC from birth to 40 weeks in cm	9.68 (2.1)	8.6 (1.38)	.007

Malnutrition at 40 weeks of cGA was lower in the TG (38% vs. 72%, p=.002). HC was larger in the TG (35.4 vs. 34.6 cm, p= .028). At one year of cGA the effect of intervention on weight was lost. Nevertheless, the gain in HC persisted up to one year after birth (20.6 vs.21.7 cm, p = .026).

Psychomotor Development



Psychomotor development: Development Scale of Evaluation of Rodríguez et al.

Univariate analyses showed that PD was 0.13 points higher in the TG (1.02 vs. 0.89, 95% CI: 0.049-0.224). This effect persisted in multivariate analyses, increasing PD by 0.094 (95% CI: 0.012-0.175) in the TG. Maternal education was a significant variable, improving the PD by 0.014 points for each year spent in school (95% CI: 0.0003-0.0283).

Conclusions

In this population, patients who received early and intensive nutritional intervention showed lower rates of postnatal undernourishment at 40 weeks cGA and better PD at one year of life. Better growth of this group might partially be explained by dietary intake even though it was impossible to avoid deficit. However, non dietary factors also affect growth in the study of Emblenton et al. 50% of the variation in growth was related to diet, and 50% was an explained. (4)
The disappearance of beneficial effects on posterior nutritional status could be interpreted as a lack of participation in any nutritional program on the part of the high risk population after leaving the hospital. The correlation between better education of the mother and improved neurological development in her child might be the consequence of such factors as a favorable environment providing more intellectual stimulation and a better use of health care resources.

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