Hypercalcemia and hypophosphatemia among preterm infants receiving aggressive parenteral nutrition

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ABSTRACT

Introduction. Aggressive parenteral nutrition is the standard of care among very-low-birth weight preterm infants. However, in recent studies, its impact on short-term outcomes, has been evaluated. The objective was to compare the prevalence of hypercalcemia and hypophosphatemia among preterm infants receiving aggressive or standard parenteral nutrition.

Methods. Observational, retrospective study comparing a group of preterm infants weighing less than 1250 grams who received aggressive parenteral nutrition with a historical control group. The prevalence of hypercalcemia was estimated and its association with aggressive parenteral nutrition was searched adjusting by confounders. The mean phosphate level was estimated for the control group by linear regression and was compared to the value in the other group.

Results. Forty patients per group were included. The prevalence of hypercalcemia was higher in the group who received aggressive parenteral nutrition (87.5% versus 35%, p= 0.001). Aggressive parenteral nutrition was associated with hypercalcemia when adjusting by birth weight, intrauterine growth restriction, amino acid, and calorie intake (adjusted odds ratio: 21.8, 95% confidence interval [CI]: 3.7-128). The mean calcium level was different between both groups (p= 0.002). Infants who received aggressive parenteral nutrition had more sepsis without reaching statistical significance and the mean phosphate level was lower than that estimated for the control group (p= 0.04). The prevalence of hypophosphatemia in this group was 90% (95% CI: 76-97%).

Conclusions. Our data show an association between hypercalcemia/hypophosphatemia and aggressive parenteral nutrition. It is recommended to frequently monitor calcium and phosphate levels since they might be associated with adverse clinical outcomes.

Key words: *hypercalcemia, hypophosphatemia, parenteral nutrition, preterm infant.*

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INTRODUCTION

It has been widely shown that the preterm newborn infant (PTNI) (birth weight [BW] < 1500 grams) has a high risk of developing postnatal growth restriction,[1,2] which still is a frequent complication in spite of recommendations about an early and adequate nutrition. The strategy that combines early and aggressive parenteral nutrition (PN), including a high energy nutrition plan from the first day of life, with the administration of human milk, has become the standard of care.[3,5] It has been shown that this approach improves the nutrition status of preterm patients[4,6,7] and reduces the potential long-term negative impact of nutritional deficiency; mainly on neurodevelopment.[8,9] However, recent research studies have focused on the impact of this nutritional strategy on short-term outcomes, like mineral and electrolyte homeostasis, especially in the phosphocalcic metabolism.[10-13] Besides, in this group of patients, aggressive PN has been associated with a higher incidence of sepsis.[9,14]

The main cause of this disturbance could be a suboptimal calcium and phosphorus supplementation.[15,16] Additionally, the refeeding syndrome, defined by the presence of hypophosphatemia, hypercalcemia, and hypokalemia, has been associated with an early, high-caloric nutrition.[10,17] According to what has been reported by some authors, the high amino acid intake in the first week of life is the main factor related to blood calcium and phosphorus levels.[10,11] Besides, this disorder has mainly been associated with intrauterine growth restriction (IUGR).[10,12,17] PTNIs included in

aggressive nutritional support are in an anabolic state, thereby they consume higher energy which might lead to a higher use of phosphorus.[10]

The present study has been developed to have a better understanding of its causality. A PTNI cohort who received aggressive PN with a high prevalence of the disorder was compared with a historical control group of patients who received standard PN. Our hypothesis was that this was associated with an aggressive PN. The main objective was to compare the prevalence of hypercalcemia and hypophosphatemia during the first week of life between both groups.

METHODS

Design: Retrospective, observational, and analytical study that compared two groups of similar patients, except for the PN administered.

Study population: PTNIs with a birth weight of less than 1250 grams were eligible to be included in the study:

Group 1: PTNIs born between January 2012 and December 2014 who received aggressive PN.

Group 2: PTNIs born between January 2008 and December 2010 who received standard PN.

Exclusion criteria: Patients whose calcium levels had not been measured during the first week of life, those with major congenital malformations or who had died in the delivery room or within the first hours of life. Patients born in 2011 (year when aggressive PN was implemented) were also excluded because of a likely overlapping of both strategies.

Exposure: Patients in Group 1 received PN with 3 to 4 g/kg/day of amino acid intake (AMINOVEN INFANT 10%), 2 to 3 g/kg/day of lipid 20% supplementation (Lipovenoes MCT/LCT 20% or SMOF® lipid 20%) from the first day of life (PN by Fresenius Kabi®, Buenos Aires, Argentina). Patients in the historical Group 2 received PN with 2-3 g/kg/day of the same amino acids and 0.5-2 g/kg/day of the same lipids from the second or third day of life on. In both groups, the formula consisted of a 3-in-1 solution which included dextrose, amino acids, and lipids. No other changes were done in the PN composition besides those previously described. Calcium gluconate (40 mg/kg/day) and glycerophosphate (20 mg/ kg/day) were used at a ratio of 2:1 (molar 1.5:1), which was constant in both periods.

Measurements: Ionized calcium and phosphate levels were collected (corresponding to the first week of life) from each patient's electronic case record. For the analysis, the lowest phosphate level and the highest calcium level were recorded for each patient, as well as the mean values of both. Ionized calcium levels were reported in mmol/L (1 mmol/L = 4.01 mg/dl) and phosphate levels in mg/dl (3.1 mg/dl= 1 mmol/L).

Primary outcome measure: The prevalence of hypercalcemia between both groups was compared. It was defined as a serum ionized calcium level above 1.35 mmol/L.

Serum phosphate level: It was not available for the historical group, since in those days, it was not measured systematically during the first week of life. However, the historical mean phosphate level was estimated using a linear regression model derived from our previously reported cohort.[13] Hypophosphatemia was defined as every value below 4 mg/dL.

Demographic outcome measures: Data were collected on IUGR, defined as a BW lower than 10% for the gestational age (GA); GA, defined as the date of the last menstrual period (LMP), and BW. Besides, mean calorie and amino acid levels received by each patient to ensure that the exposure outcome measure was different between both groups.

Short-term outcome measures: The need of assisted mechanical ventilation (AMV), the use of inotropes, and the presence of sepsis were compared between both groups.

Statistical analysis: Measures of central tendency and dispersion were calculated for continuous outcome measures. These data were reported as mean (standard deviation [SD]) or median (interquartile range [IQR]) according to the distribution and were compared between both groups by means of the Student's t or Mann-Whitney tests, as appropriate. Both hypercalcemia and other dichotomous outcome measures were expressed as a percentage and were compared using the χ^2 test. A univariate analysis was performed to evaluate the association between aggressive PN and hypercalcemia. Then, a logistic regression analysis was performed adjusting for confounding outcome measures, such as BW, IUGR, amino acid and calorie intake. Linear regression was used based on data on phosphate and calcium levels in group 1 with which the phosphate level could be estimated in terms of the calcium level (taking into account that there was a significant negative correlation between both). Then, the theoretical mean phosphate level of the historical group was estimated in terms of the mean calcium level in this group. A value of

$p < 0.05$ was considered significant.

Sample size calculation: Taking into account the previously published article,[13] in which a prevalence of 80% of hypercalcemia was reported in patients with aggressive PN, estimating a prevalence of 50% (since it was unknown) in the historical group, with a power of 80% and an alpha value of 5%, it was necessary to include 40 patients per group. They were selected by simple random sampling. The statistical analysis was performed with the Stata 13 software.

Ethical considerations: The study was approved by the Ethics Committee for Research Protocols of our hospital.

RESULTS

During the study period, 164 PTNIs were born at our hospital with a birth weight of less than 1250 grams. Twenty-eight infants born in 2011 were excluded, 11 patients who died in the first 48 hours of life and/or had congenital malformations and 5 in whom calcium levels had not been measured. After applying said inclusion criteria, 120 PTNIs remained eligible for the study and 40 patients per group were selected.

The mean GA and BW of the total population were 27.3 ± 2.4 weeks and 894 ± 192 grams, respectively; no differences were found when comparing them between both groups. *Table 1* depicts demographic and short-term outcome measures comparing both groups. PTNIs who received standard PN required AMV and vasoactive drugs more frequently. Sepsis incidence was higher in the group treated with aggressive PN without reaching statistical significance. Hypercalcemia prevalence was significantly higher in patients who received aggressive PN. Aggressive PN was associated with hypercalcemia (odds ratio [OR]: 13, 95% confidence interval [CI]: 4.1-41, $p= 0.001$). Mean ionized calcium level (mmol/L) was different between both groups: 1.25 ± 0.10 versus 1.13 ± 0.16, $p= 0.002$ (*Figure 1*). Mean phosphate level in group 1 was 3.35 ± 1.47 mg/dl and hypophosphatemia prevalence was 90% (95% CI: 76-97%) (phosphate values were available only in this group). Then, hypercalcemic patients were compared to normocalcemic patients (*Table 2*). Patients with hypercalcemia received a higher calorie and amino acid intake. Additionally, they had a higher incidence of IUGR although this difference was not significant.

In a logistic regression model (*Table 3*), the association between aggressive PN and hypercalcemia maintained its statistical significance after adjusting for BW, IUGR, and amino acid and calorie intake (adjusted OR: 21.8, 95% CI: 3.7-128). Finally, a linear regression was done for phosphate level as a function of calcium level, using group 1 data (*Table 4*). Then, considering the mean ionized calcium value of the historical group 1.13 mmol/L (4.53 mg/dL), the mean phosphate level was estimated in this group: 4.2 mg/dl (95% CI: 2.41-5.92). The estimated mean phosphate level of the historical group was statistically higher than the phosphate level in the group that received aggressive PN: 4.2 mg/dl versus 3.35 mg/dl ($p= 0.04$).

DISCUSSION

The present study shows that both the prevalence of hypercalcemia and the mean ionized calcium level are higher in the group of patients who received aggressive PN. In our unit, this nutrition strategy started being used in 2011, which reported a high prevalence of associated

TABLE 1. *Characteristics of patients by nutritional approach*

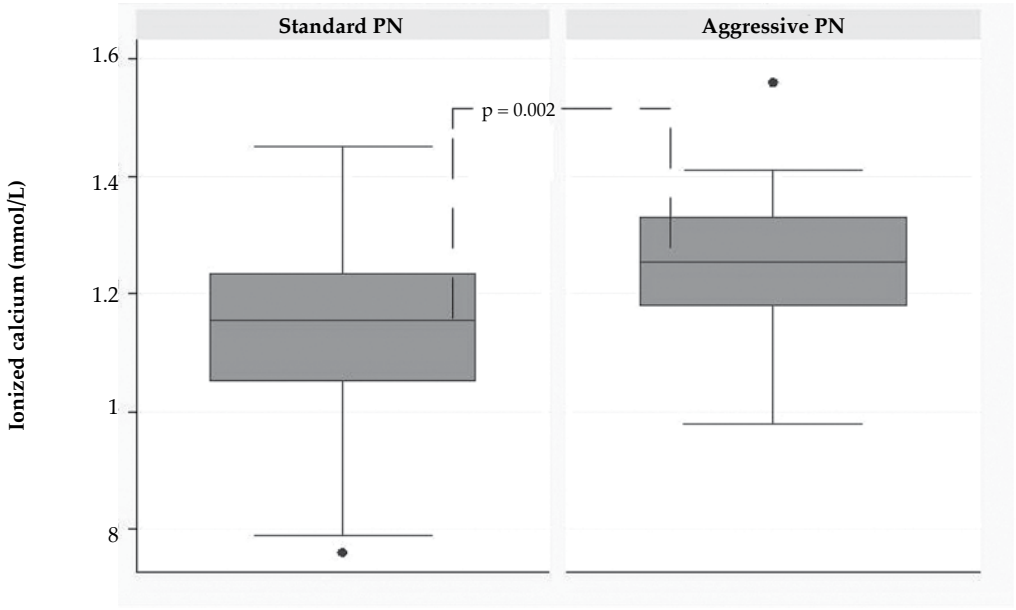
Outcome measure	Aggressive PN Group 1 (n= 40)	Standard PN Group 2 (n= 40)	*P* value
GA (weeks), median (IQR)	27.5 (26-29)	27 (25-28)	0.31 (*)
BW (grams), mean ± SD	911 ± 181	877 ± 203	0.44 (¥)
IUGR, n (%)	11 (27)	8 (20)	0.43 (Ŧ)
Hypercalcemia, n (%)	35 (87)	14 (35)	0.001 (Ŧ)
Calories (kcal/kg/day), median (IQR)	82 (74-86)	66 (57-68)	0.001 (*)
Amino acids (g/kg/day), median (IQR)	3.5 (3.3-3.7)	2.8 (2.5-3.1)	0.001 (*)
Inotropes, n (%)	8 (20)	12 (30)	0.30 (Ŧ)
AMV, n (%)	17 (42)	35 (87)	0.001 (Ŧ)
Sepsis, n (%)	12 (30)	5 (12.5)	0.054 (Ŧ)

PN: parenteral nutrition; GA: gestational age; BW: birth weight; IUGR: intrauterine growth restriction; AMV: assisted mechanical ventilation; IQR: interquartile range; SD: standard deviation.
(*) Mann-Whitney test. (¥) Student's *t* test. (Ŧ) $\chi 2$ test.

early hypophosphatemia and hypercalcemia.[13] Additionally, since it showed a negative correlation between calcium and phosphate levels within the first week of life, it is proposed that the significant difference in mean calcium levels between both groups should be accompanied by a similar difference in the mean phosphate level. Since studied demographic outcome measures (GA, BW, IUGR) were similar between both groups, while the exposure (amino acid and calorie intake) is different, the association found between hypercalcemia and aggressive PN might be causal. Besides, in the multivariate analysis, this association remained significant after having adjusted for the possible confounding factors.

There is increasing bibliography highlighting this problem and describing its likely causes.[10-18] It has been described that it may resemble what happens in the pediatric and adult population deprived of nutrients for long periods when restarting the feeding[19] and it is likely that a suboptimal calcium and phosphorus intake is the main cause of such imbalance. Moe et al. studied a group of PTNIs < 28 weeks who received different phosphate supplementations in the PN. They found that phosphate levels corresponded to phosphorus intake because those patients who received less quantity of phosphorus had the lowest phosphate level.[20]Contrary to other studies, they found that an increase in the amino

FIGURE 1. *Mean ionized calcium level by parenteral nutrition*



PN: Parenteral nutrition.

TABLE 2. *Characteristics of patients by development of hypercalcemia*

Outcome measure	Hypercalcemia (n= 49)	Normocalcemia (n= 31)	*P* value
GA (weeks), mean ± SD	27.4 ± 2.3	27 ± 2.4	0.40 (¥)
BW (grams), mean ± SD	877 ± 182	921 ± 206	0.30 (¥)
IUGR, n (%)	15 (30)	4 (13)	0.07 (Ŧ)
Calories (kcal/kg/day), median (IQR)	77 (67-84)	67 (58-71)	0.01 (*)
Amino acids (g/kg/day), median (IQR)	3.4 (3-3.5)	3 (2.7-4.4)	0.001 (*)
Inotropes, n (%)	11 (22)	9 (29)	0.50 (Ŧ)
AMV, n (%)	27 (55)	25 (80)	0.02 (Ŧ)
Sepsis, n (%)	12 (24)	5 (16)	0.30 (Ŧ)

GA: gestational age; BW: birth weight; IUGR: intrauterine growth restriction; AMV: assisted mechanical ventilation; IQR: interquartile range; SD: standard deviation.
(¥) Student´s t test. (Ŧ) $\chi 2$. (*) Mann-Whitney.

acid content in PN solutions did not seem to have any impact on weight gain during the first month of life.[20] A recently published prospective study conducted by Christmann et al. showed that both hypercalcemia and hypophosphatemia might occur after implementing PN with a higher calcium and phosphorus supplementation.[16] In a research study about a PTNI population similar to ours, Senterre et al. concluded that the higher calcium and phosphorus intake with a molar relation ≤ 1 prevented this disorder.[15] Other authors recently compared 2 groups of PTNIs who received PN with a high amino acid supplementation and also recommended to increase the intake of these minerals administering them equimolarly.[21] In our study, both groups of patients received PN (solution mix 3:1) with the same quantity of these minerals in a molar proportion of 1.5:1 (40 mg/kg/ day of calcium gluconate and 20 mg/kg/day of glycerophosphate). Therefore, it is likely that inadequate quantities were administered in an inappropriate proportion, which could be considered an important factor for the alterations found. However, both groups were exposed to this likely inadequate intake while the adverse result occurred only in the group that received aggressive PN.

Several authors found that this disorder was associated with IUGR.[10,12,17] Ross et al. recently published a retrospective cohort study at 10 years in which the refeeding syndrome occurred in PTNIs with IUGR born from mothers with preeclampsia, with this outcome adjusted to the nutritional care practice.[17] Even more, they showed a relationship between brochopulmonary dysplasia and hypophosphatemia.[17] In our previous study, 40% of patients with hypophosphatemia had IUGR.[13] In the present study, patients with hypercalcemia had more IUGR; however, this association was not statistically significant.

The "refeeding syndrome" resulting from aggressive PN might cause hypophosphatemia, hypercalcemia, and hypokalemia according to some authors.[11,12] The high intake of amino acids during the first week of life was the determining factor of calcium and phosphorus levels in an analysis about the intake of different macronutrients.[11] In the present study, a strong association between aggressive PN and hypercalcemia has been shown adjusting for other related outcome measures. The concept of aggressive PN implies starting at an early stage after birth with a high intake of amino acids and lipids. Since amino acid intake did not reach a statistical significance in our multivariate model, it is likely that other characteristics of aggressive PN, like lipid intake or the time elapsed since birth to the start of PN (which was different in both groups), are involved in this concept.

There is a potential impact of this disorder in PTNIs. Phosphorus is essential in the generation of adenosine triphosphate (ATP); therefore, its

TABLE 3. *Univariate and multivariate analyses: odds ratio and adjusted odds ratio of presenting hypercalcemia*

Outcome measure	Univariate analysis OR (95% CI)	Multivariate analysis aOR (95% CI)	*P* value
BW	0.99 (0.99-1)	0.99 (0.98-1)	0.1
IUGR	2.98 (0.88-10)	0.83 (0.10-6.62)	0.2
Kcal/kg/día	1.07 (1-1.12)	1.05 (0.97-1.14)	0.1
Amino acids	3.71 (1.3-10)	0.24 (0.03-1.48)	0.1
Aggressive PN	13 (4.1-41)	21.8 (3.72-128)	0.001

BW: birth weight; IUGR: intrauterine growth restriction; PN: parenteral nutrition; OR: odds ratio; aOR: adjusted odds ratio; CI: confidence interval.
Adjusted by BW, IUGR, amino acids, kcal, and aggressive PN.

TABLE 4. *Linear regression equation for phosphate levels as a function of calcium levels. Number of observations: 244*

Coefficient	95% confidence interval	Standard error	*P* value
β_0= 8.9	De 7.9 a 10.1	0.406	0.001
B_1= -4.3	De -5.1 a -3.5	0.543	0.001

Regression equation: $Y = \beta 0 + \beta 1\ X$.
Pairs of data of calcium and phosphate levels of group 1 were used.
R^2= 0.32; p = 0.0001.

deficit has a direct effect on cell metabolism.[13,19,22] Neuromuscular weakness and extubation failure have been described in adult patients with hypophosphatemia,[22,23] and a recent report about a PTNI with a low birth weight for GA that developed bradycardia, respiratory failure, and hemolytic jaundice attributes this condition to an inadequate intake of phosphorus and to the refeeding syndrome triggered by the aggressive PN.[24] Even more, recently, respiratory morbidity (severe bronchopulmonary dysplasia) has been associated with early hypophosphatemia in preterm infants with a very low BW.[25,26] However, in this study, all PTNIs fed with standard PN (normocalcemic patients) required AMV more frequently. This might reflect a change in the clinical practice during recent years regarding respiratory management in our neonatal care unit, with greater use of non-invasive ventilation. Besides, phosphorus takes part in the migration of immune cells and phagocytes. A randomized study comparing two nutritional strategies had to be interrupted because a higher rate of sepsis was found in patients fed with aggressive PN.[13] In our study, patients who received aggressive PN had a higher incidence of sepsis, although this difference was not statistically significant.

Our study poses limitations. Apart from the studied aspects of neonatal care, other factors (like the respiratory management mentioned before) might have changed between both periods. This could also account for the results found, besides the exposure outcome measure. Due to the retrospective and observational design of this study, causality cannot be established in an absolute manner. However, our data firmly support the studied association. Besides comparing calcium values, it would have been appropriate to do the same comparison with phosphate levels but phosphate has not been measured historically. Since the comparison was not done on real databases, it is difficult to ensure causality. Anyhow, a high prevalence of hypophosphatemia associated to aggressive PN was observed.

To conclude, according to our data, there is an association between hypercalcemia/hypophosphatemia and aggressive PN in preterm patients with a very low birth weight. A frequent monitoring of calcium and phosphorus levels is recommended in PTNIs receiving aggressive PN since it can be associated with an adverse clinical outcome. ■

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