Residência Pediátrica
Publicação Oficial da Sociedade Brasileira de Pediatria
ISSN-Online: 2236-6814

Submitted on: 09/27/2021
Approved on: 10/14/2021

REVIEW ARTICLE

Supplementation of vitamins and minerals in premature newborn: An integrative literature review

Daniella Ramiro Vittorazzi[1], Clarissa Paneto Sulz[1], Larissa Pandolfi Soares[1]

Keywords:
Infant,
Premature,
Vitamins,
Vitamin A,
Iron,
Infant,
Low Birth Weight,
Vitamin.

Abstract

Introduction: Premature newborns (PTNB) generally have micronutrient deficiencies. This fact is justified due to low stocks, insufficient diet and increased metabolic needs. Therefore, it is important to supplement with vitamins and minerals in the perinatal period and in the outpatient follow-up of these babies. **Objective:** To evaluate the supplementation of vitamins and minerals in PTNB, highlighting its risks and benefits. Consider the indication and maintenance of supplements on an outpatient basis during follow-up. **Methods:** Integrative review in PubMed, LILACS and SciELO databases. For the research, 473 articles were identified in English and Portuguese, published between 2012 and 2020. Of these, 16 articles were selected for the study. **Results:** The benefit of vitamin A is greatly reduced and further analysis is needed. About vitamin D, most studies have shown that 400IU achieve adequate bone mineralization. Research has shown no significant effect on the use of calcium and phosphorus in preventing osteopenia. Regarding zinc supplementation, the only study found showed an improvement in growth in extremely low birth weight babies with chronic lung disease. However, ESPGHAN and SBP recommend its routine use for preterm in general. Iron deficiency is the most common nutritional deficiency in childhood and is associated with impaired neurodevelopment, so its supplementation is highly recommended. **Conclusion:** PTNB are a risk group for vitamin and mineral deficiency. There are few studies on routine supplementation, so the current recommendations, the SBP and ESPGHAN consensus, should be considered.

[1] Hospital Santa Casa de Misericórdia de Vitória , Pediatric Medical Residence - Vitória - Espírito Santo - Brazil.

Correspondence to:
Daniella Ramiro Vittorazzi.
Hospital Santa Casa de Misericórdia de Vitória. R. Dr. João dos Santos Neves, nº 143, Vila Rubim.
Vitória - ES. Brasil. CEP: 29025-023. E-mail: daniellaramiro1@gmail.com

DOI: 10.25060/residpediatr-2022.v12n4-738

This work is licensed under a Creative Commons Attribution 4.0 International License.

INTRODUCTION

Premature newborns (PTNB) generally present micronutrient deficiency. This fact is justified by the fact that they have low stocks, which would be formed in the 3rd trimester of pregnancy, in addition to their insufficient diet and increased metabolic needs. Therefore, the supplementation of vitamins and minerals in the perinatal period and in the outpatient clinical follow-up of these babies becomes important.

Current vitamin and mineral supplementation recommendations in Brazil come from the Brazilian Society of Pediatrics, the American Academy of Pediatrics (AAP) and the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), with certain differences between doses and duration of supplementation.

In this systematic review, these divergences were unraveled, seeking to reach a consensus on the best way to supplement a PTNB. In addition, several articles focused on this topic were analyzed to provide a greater basis for the discussion.

METHODOLOGY

The research was elaborated from an integrative review, in which the following guiding question was established: "What are the peculiarities reported by the literature on vitamin and mineral supplementation in premature newborns?".

A total of 473 articles were identified in the PubMed, LILACS, SciELO databases, and only 16 were selected for the study. The following descriptors were used: "premature" (preterm infants), "supplementation" (supplementation), "vitamins" (vitamins), "newborns" (newborns). The inclusion criteria adopted by the present study were the publication having supplements for preterm NB as its theme; reviews published in English and Portuguese; complete publications with abstracts available and indexed in the databases and comprised the years of publication between 2012 and 2020. Studies with non-pediatric patients, such as pregnant women, were excluded, as well as studies that did not address the topic relevant to the purpose of the review.

RESULTS

Vitamin A (Retinol)

This vitamin maintains the integrity of the respiratory epithelium and regulates cell differentiation; thus it appears to be promising in the prevention of bronchopulmonary dysplasia. It is an essential micronutrient, which in small doses, helps in the proper functioning of the visual system, immune function, antioxidant defense, among others.

Garofoli et al[1] analyzed 41 PTNB with very low birth weight, where 31 received 3,000 IU/kg/day of vitamin A, while 10 did not receive supplementation of this vitamin. It was concluded that the use of vitamin A had no impact on the prognosis and development of pathologies typical of prematurity bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC) and late-onset sepsis.

Chandrasekaran and Murki[2], in an analytical study, observed that oral vitamin A is superior to intramuscular (IM) vitamin A only as a route of administration since oral vitamin A did not result in the prevention of BPD or death. The IM form, despite having reduced BPD by 7%, is extremely painful, can cause local infection and still has difficult applicability in PTNB due to the low muscle density.

Basu et al[3], in a randomized, double-blind, placebo-controlled study, evaluated the effects of oral vitamin A supplementation in 196 infants who required positive pressure respiratory support (CPAP). The result showed that there was a lower incidence of patent ductus arteriosus (PDA), respiratory distress syndrome (RDS) and early sepsis in the group receiving vitamin A compared to the placebo group.

Darlow et al[4] in an original review evaluated retinol supplementation. The result obtained was that in relation to the control group, the group supplemented with vitamin A showed little benefit in relation to the decrease in the need for oxygen at 01 month of age and the risk of chronic lung disease.

Both Uberos[5] et al and Yang[6] found in their studies that there is no similar benefit of retinol for preventing the incidence of BPD. These authors reported in their work that the risk of sepsis in PTNB with vitamin A supplementation was three times higher compared to premature babies who did not receive this supplementation.

In an original article, Gregory[7] concludes that vitamin A supplementation has been shown to be beneficial in extremely low birth weight babies, but the benefit found is small and further studies are needed to understand which babies would benefit from supplementation. In addition, the decision to establish intramuscular injections of vitamin A as a prevention of BPD will depend on the incidence of this comorbidity in each Neonatal Intensive Care Unit (NICU).

With this, it is noted that the use of vitamin A is still controversial, as well as its dose and route of administration.

Iron

Iron is an essential mineral for brain development and prevention of important iron deficiency, in addition to being a fundamental substrate for hematopoiesis.

Freitas et al[8], analyzed in a prospective cohort study with 58 preterm infants born in 2014 until they reached six months of corrected age, and verified adherence to guidelines for iron, zinc and multivitamin supplementation recommendations, and the influence on the occurrence of anemia and deficiency of iron, zinc, and vitamin A. A higher prevalence of anemia and iron deficiency was observed in the group with low adherence, but also relevant in the group with high adherence. Premature infants in the group with low adherence to micronutrient supplementation were 2.5 times more likely to develop anemia.

Oliver et al[9], evaluated current mineral and vitamin supplementation practices in neonatal intensive care units and special care nurseries in Australia and New Zealand, and found that iron supplementation is universal among neonatal units, but the dose, the duration, and the ideal moment for the realization, have not yet been elucidated.

McCarthy et al[10], performed a systematic review to investigate the effects of enteral iron supplementation on neurological development and growth in low birth weight (<2500g) and preterm infants, where it was observed that long-term iron supplementation leads to a decrease in of anemia and iron deficiency, but high-quality evidence on long-term effects on functional health outcomes is lacking.

ESPGHAN[11] recommends enteral iron supplementation of 2-3 mg/kg/day, starting at 2-6 weeks of age. Infants receiving erythropoietin treatment or with significant and uncompensated blood loss may require a higher dose. Enteral doses greater than 5 mg/kg/day should be avoided in premature infants due to the possibility of retinopathy of prematurity. Iron supplementation should be maintained, at least until 6-12 months of age, depending on the diet.

The Brazilian Society of Pediatrics[12] of advises that iron supplementation in preterm newborns should be started after 30 days of life, with 2 mg/kg/day for babies weighing between 1,500 and 2,500 g, 3 mg/kg/day for babies weighing between 1,500 and 2,500 g, between 1,000 and 1,500g, and 4 mg/kg/day with a weight of less than 1,000g, for one year, after that period, 1 mg/kg/day for another year in all cases.

Vitamin D

Vitamin D is a prohormone that acts in the metabolism of calcium and phosphorus, contributing to bone growth and mineralization. PTNBs constitute one of the risk groups for hypovitaminosis D, which is why it is important to assess the need for supplementation in these NBs.

In addition, vitamin D is an important regulator of cellular immunity, which favors the ideal development of these babies.

Most studies on vitamin D supplementation in preterm infants are evaluating the best dose to be given to these patients, in addition to their advantages and disadvantages.

The study by Mathur et al[13] compared the effect of supplementation with 400 IU and 1000 IU of vitamin D for 6 weeks in very low birth weight preterm births. The result found was that those who used 1000 IU of Vitamin D had a lower rate of skeletal hypo mineralization, weight, and height growth than those who used 400 IU.

As for Abrams[14], in his research, the author reports that a routine assessment of bone mineral content should be carried out using biochemical tests, so that supplementation can subsequently be carried out according to the needs in NB <1,500g. Testing should usually start 4 to 5 weeks after birth. For those with more than 1,500 g and who tolerate enteral feeding, the recommendation is for the daily intake of vitamin D to be from 400 IU to a maximum of 1000 IU.

Salas et al[15], in a study that determined the dose-response relationship between increasing doses of enteral vitamin D in the first 28 days after birth and cognitive scores at 2 years of age. The result found was that there was no significant difference in cognitive scores in babies who used high or low doses of vitamin D.

Oliver et al[9], showed that the use of 400 IU of vitamin D achieves adequate mineralization in premature babies when compared with higher doses of 800-1000 IU/day.

Anderson-Berry et al[16], in a randomized double-blind study, evaluated the effects of two different doses (400 IU x 800 IU) of vitamin D in a population of premature patients during NICU stay in relation to improvement in growth, normalization of PTH and bone density. It is likely that for a PTNB ratio a dose of 400 IU is adequate for normal cell and tissue function, however, there is a small proportion of the population that does not respond exactly to this dose and in which a higher dose such as 800 IU or 1200 UI can be advantageous.

The American Academy of Pediatrics recommends supplementing 400 IU/day, while ESPGHAN recommends 800-1000 IU/day.

These more recent studies have analyzed the ideal dose, but the results are not yet conclusive.

Zinc

height growth. According to the Brazilian Society of Pediatrics, zinc supplementation with 5 mg/day for six months significantly improves neuronal development and linear growth in very low birth weight preterm infants. The SPB recommendation is to start at 36 weeks of corrected age and maintain it for up to 6 months of corrected age.

In a cohort study, Shaikhkhalil et al[17], observed preterm infants with chronic lung disease (BPD) from January 2008 to December 2011, with zinc supplementation for at least 14 days, and found that after one week of supplementation of this mineral, these babies showed a considerable evolution in weight and height gain.

Calcium and Phosphorus

Preterm neonates are at greater risk of developing metabolic bone disease (MBD) than term newborns due to changes in calcium and phosphorus metabolism. This is because the greatest increase in calcium and phosphorus occurs in the third trimester of pregnancy, consequently, premature infants who are not adequately supplemented with vitamin D, calcium and phosphorus may have osteopenia and/or rickets.

Torabi et al[18], in a randomized clinical trial, failed to obtain any evidence to suggest the effectiveness of calcium and phosphorus supplementation in osteopenia of prematurity. In addition, it concluded that further studies with different doses of supplements and for a longer period are needed to arrive at an effective protocol.

The recommended oral calcium intake ranges from 140-160 mg/100 Kcal (American Academy of Pediatrics) and 70-140 mg/Kg/day per 100 Kcal (European Society of Pediatric gastroenterology and Nutrition). The Brazilian Society of Pediatrics currently recommends calcium 100-160 mg/Kg/day and phosphorus 95-108 mg/Kg/day per 100 Kcal.

Both breast milk and infant formulas do not provide the necessary amount of these elements, requiring addition to the diet. The ideal calcium/phosphorus ratio for bone mineralization is 1.7:1. In case of positive screening for MBD, calcium and phosphorus supplementation should continue after discharge with a compounded solution. The total daily intake should be 200-250 mg/kg/day of calcium and 110-125 mg/kg/day of phosphorus.

DISCUSSION

After selecting and reading these articles, observed that there is still a great divergence between the performance or not of vitamin and mineral supplementation in premature babies. It is noted that most authors recommend supplementation even in the absence of strong evidence, as well as the European, American, and Brazilian societies of pediatrics.

In Brazil, the recommendations of the Brazilian Society of Pediatrics are mainly followed, with supplementation of vitamin D, iron, polyvitamins (complex with vitamins A, C, D and complex B) and zinc. Calcium and phosphorus supplementation is reserved for preterm infants who have metabolic bone disease.

REFERENCES

1. Garofoli F, Mazzucchelli I, Decembrino L, Bartoli A, Angelini M, Broglia M, et al. Levels and effectiveness of oral retinol supplementation in VLBW preterm infants. Int J Immunopathol Pharmacol. 2018;32:2058738418820484.
2. Chandrasekaran A, Murki S. Is early oral vitamin A supplementation useful in preterm neonates at risk for bronchopulmonary dysplasia? Acta Paediatr. 2020;109(3):634-5.
3. Basu S, Khanna P, Srivastava R, Kumar A. Oral vitamin A supplementation in very low birth weight neonates: a randomized controlled trial. Eur J Pediatr. 2019;178(8):1255-65. DOI: 10.1007/s00431-019-03412-w
4. Darlow BA, Graham PJ, Rojas-Reyes MX. Vitamin A supplementation to prevent mortality and short- and long-term morbidity in very low birth weight infants. Cochrane Database Syst Rev. 2016;2016(8):CD000501. DOI: 10.1002/14651858.CD000501.pub4
5. Uberos J, Miras-Baldo M, Jerez-Calero A, Narbona-López E. Effectiveness of vitamin A in the prevention of complications of prematurity. Pediatr Neonatol. 2014;55(5):358-62.
6. Yang SN. Nutritional approach to the prevention of complications of prematurity with emphasis on vitamin A supplementation. Pediatr Neonatol. 2014;55(5):331-2.
7. Gregory KE. Vitamin A supplementation: is it worth a shot? J Perinat Neonatal Nurs. 2014;28(4):253-5.
8. Freitas BA, Lima LM, Moreira ME, Priore SE, Henriques BD, Carlos CF, et al. Micronutrient supplementation adherence and influence on the prevalences of anemia and iron, zinc and vitamin A deficiencies in preemies with a corrected age of six months. Clinics (Sao Paulo). 2016;71(8):440-8.
9. Oliver C, Watson C, Crowley E, Gilroy M, Page D, Weber K, et al. Vitamin and Mineral Supplementation Practices in Preterm Infants: A Survey of Australian and New Zealand Neonatal Intensive and Special Care Units. Nutrients. 2019;12(1):51. DOI: 10.3390/nu12010051
10. McCarthy EK, Dempsey EM, Kiely ME. Iron supplementation in preterm and low-birth-weight infants: a systematic review of intervention studies. Nutr Rev. 2019;77(12):865-77.
11. Agostoni C, Buonocore G, Carnielli VP, De Curtis M, Darmaun D, Decsi T, et al; ESPGHAN Committee on Nutrition. Enteral nutrient supply for preterm infants: commentary from the European Society of Paediatric Gastroenterology, Hepatology and Nutrition Committee on Nutrition. J Pediatr Gastroenterol Nutr. 2010;50(1):85-91. DOI: 10.1097/MPG.0b013e3181adaee0
12. Sociedade Brasileira de Pediatria (SBP). Manual seguimento ambulatorial do prematuro de risco / Rita de Cássia Silveira. 1ª ed. Porto Alegre: Sociedade Brasileira de Pediatria. Departamento Científico de Neonatologia; 2012. Disponível em: http://www.sbp.com.br/pdfs/Seguimento_prematuro_oficial.pdf
13. Mathur NB, Saini A, Mishra TK. Assessment of Adequacy of Supplementation of Vitamin D in Very Low Birth Weight Preterm Neonates: A Randomized Controlled Trial. J Trop Pediatr. 2016;62(6):429-35.
14. Abrams SA; Committee on Nutrition. Calcium and vitamin d requirements of enterally fed preterm infants. Pediatrics. 2013;131(5):e1676-83.
15. Salas AA, Woodfin T, Phillips V, Peralta-Carcelen M, Carlo WA, et al. Dose--Response Effects of Early Vitamin D Supplementation on Neurodevelopmental and Respiratory Outcomes of Extremely Preterm Infants at 2 Years of Age: A Randomized Trial. Neonatology. 2018;113(3):256-62. DOI: 10.1159/000484399

16. Anderson-Berry A, Thoene M, Wagner J, Lyden E, Jones G, Kaufmann M, et al. Randomized trial of two doses of vitamin D3 in preterm infants <32 weeks: Dose impact on achieving desired serum 25(OH) D3 in a NICU population. PLoS One. 2017;12(10):e0185950. DOI: 10.1371/journal.pone.0185950

17. Shaikhkhalil AK, Curtiss J, Puthoff TD, Valentine CJ. Enteral zinc supplementation and growth in extremely-low-birth-weight infants with chronic lung disease. J Pediatr Gastroenterol Nutr. 2014;58(2):183-7.

18. Torabi Z, Moemeni N, Ahmadiafshar A, Mazloomzadeh S. The effect of calcium and phosphorus supplementation on metabolic bone disorders in premature infants. J Pak Med Assoc. 2014;64(6):635-9.