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PARENTERAL NUTRITION IN NEONATAL CARE: INFLUENCES OF THE TIME OF INITIATION ON THE GROWTH AND CLINICAL COMPLICATIONS

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Abstract: Objective: To evaluate the effects of early or late initiation of parenteral nutrition (PN) in neonates, considering metabolic markers, oxidative stress, growth and complications, through a literature review. Methodology: A literature review based on the PVO strategy, using the keywords "Term Neonates", "Late Preterm Infants", "Neonates" and "Parenteral Nutrition". The search was carried out in the PubMed database, resulting in the selection of 29 articles for analysis. Results: The findings highlight the importance of PN in the nutritional support of preterm neonates, ensuring energy supply when enteral nutrition is not feasible. However, its administration is associated with clinical challenges, including the risk of metabolic and infectious complications, as well as the need to adjust nutritional composition to avoid deficiencies and metabolic overload. Early introduction of NP can prevent malnutrition, but without proper monitoring, it can lead to adverse effects, such as hyperglycemia and liver dysfunction. The review highlights the need for evidence-based guidelines to optimize the safety and efficacy of PN in neonates. Conclusion: PN is an essential strategy for the nutritional support of preterm neonates, reducing the risks of malnutrition and compromising growth and the immune system. However, its prolonged use can lead to complications such as cholestasis, hepatic steatosis and micronutrient deficiencies. Therefore, the decision on its introduction and maintenance should be a careful one, based on an individualized assessment of the patient. Future studies are needed to determine the ideal composition and the most appropriate time to start NP, as well as the formulation of guidelines to standardize its clinical application.

Keywords: Parenteral nutrition, neonates, newborns, nutritional support.

INTRODUCTION

Parenteral nutrition (PN) represents a significant advance in neonatal medicine and is an essential strategy to ensure adequate nutrition for premature newborns and those with compromised enteral feeding. For Prusakov, Speaks and Magers (2020), the use of PN in moderately preterm neonates has been debated, especially in relation to its effectiveness in promoting postnatal growth and preventing metabolic complications. However, the indiscriminate use of PN can result in metabolic complications and a questionable impact on neonatal development, requiring a careful assessment of the risks and benefits.

The clinical practice of PN in neonates is not homogeneous and varies according to institutional guidelines and the experience of neonatologists. (2024), there is a great disparity in the nutritional approach to extremely preterm neonates, reflecting the lack of a standardized protocol for the administration of fluids, macronutrients and essential trace elements. This variability can compromise the optimization of care and favor the occurrence of nutritional deficiencies or excesses that impact neonatal homeostasis. In addition, the safety of PN has been questioned due to the presence of contaminants such as phthalates, potentially toxic substances that can affect neurodevelopment, as demonstrated by Al-Saleh et al. (2023), who reported a negative association between exposure to phthalates and fine motor development in preterm newborns.

The influence of the timing of the introduction of PN has also been widely debated, since its early initiation can present both advantages and risks. According to Moon et al. (2024), neonates who received early PN showed better postnatal growth, but also a higher incidence of hyperglycemia. Assessing the metabolic impact of PN is fundamental to determining the balance between adequate nutritional supply and metabolic complications arising from the early use of energy substrates. This debate also extends to the monitoring of parenteral lipids. According to Bader et al. (2021), the assessment of random serum triglycerides is sufficient to monitor lipid tolerance in neonates, reducing the need for invasive tests and optimizing clinical management.

Concern about the long-term effects of PN is not limited to metabolic parameters and growth, but also to neurocognitive development. According to Terrin et al. (2021), premature neonates who received a more energetic PN in the first week of life were at greater risk of motor and socio-emotional alterations at 24 months of age. This finding reinforces the need for careful nutritional planning to ensure adequate development without metabolic or neurobehavioral damage. Therefore, drawing up nutritional guidelines that balance the supply of nutrients, preventing both deficits and excesses, is a critical aspect of neonatology.

Given this context, this study aims to evaluate, through a literature review, the impacts of the timing of starting PN (early versus late) in term and late preterm neonates, focusing on metabolic markers, oxidative stress, postnatal growth and metabolic complications, in order to provide subsidies for evidence-based neonatal clinical practice.

METHODOLOGY

A literature review developed according to the criteria of the PVO strategy, which stands for: population or research problem, variables and outcome. This strategy was used to develop the research question "What is the influence of the timing of parenteral nutrition initiation (early versus late) in term and late preterm neonates on metabolic markers, oxidative stress, postnatal growth and metabolic complications?". The searches were carried out using the PubMed - MEDLINE (Medical

Literature Analysis and Retrieval System Online) databases. The search terms were used in combination with the Boolean terms "AND" and "OR", using the following search strategy: ((“Term Neonates”)OR (“Late Preterm Infants”) OR (“Neonates”)) AND (“Parenteral Nutrition”). From this search, 401 articles were found, which were then submitted to the selection criteria. The inclusion criteria were: articles in English; published between 2021 and 2025 and which addressed the themes proposed for this research, studies of the type (narrative review, systematic review, meta-analysis, observational studies, experimental studies. The exclusion criteria were: duplicate articles, articles available in abstract form, articles that did not directly address the proposal studied and articles that did not meet the other inclusion criteria. After applying the search strategy to the database, a total of 37 articles were found. After applying the inclusion and exclusion criteria, 29 articles were selected from the PubMed database to make up this study's collection.

DISCUSSION

BENEFITS AND CHALLENGES OF PARENTERAL NUTRITION IN NEONATES

Parenteral nutrition (PN) plays a fundamental role in the nutritional support of neonates, especially in cases of extreme prematurity or when enteral feeding is not viable. According to Moon et al. (2022a), PN has the ability to meet the energy and metabolic needs of these patients, ensuring an adequate supply of macronutrients essential for early growth and development. However, its implementation involves clinical and metabolic challenges, such as infections associated with the central venous catheter, liver alterations and metabolic disorders. According to Webbe et al. (2022), prolonged exposure to PN can lead to the development of associated cholestasis, compromising liver function. Nguyen et al. (2024) point out that PN can lead to atrophy of the intestinal mucosa and a reduction in microbial diversity, making the transition to enteral feeding more difficult.

According to Johnson et al. (2022), early administration of PN can reduce the risk of malnutrition, preventing nutritional deficiencies that could compromise the growth and immune function of neonates. However, inadequate PN can result in metabolic overload, leading to hyperglycemia and metabolic acidosis, worsening the clinical picture. He et al. (2024) point out that new formulations of lipid emulsions, such as those based on fish oil, can reduce inflammation and improve liver parameters in neonates under prolonged PN. To mitigate the adverse effects of PN, strategies include careful selection of the nutritional composition and the use of minimal enteral nutrition to stimulate the gastrointestinal tract.

Moltu et al. (2021) point out that the decision on the start and duration of PN should be based on a careful assessment of the neonate's clinical status and individual needs, ensuring a balance between preventing nutritional deficiencies and minimizing the associated risks. Thus, it is essential that PN is implemented carefully, with constant monitoring and strategies to facilitate the transition to enteral feeding whenever possible.

OPTIMIZATION STRATEGIES AND PROTOCOLS FOR NP

Parenteral nutrition (PN) plays an essential role in the care of premature neonates, ensuring adequate nutritional support when enteral nutrition is not feasible, although it involves significant challenges, such as the risk of metabolic and infectious complications, requiring well-established protocols for its administration (Kriz et al., 2020). The

impact of prematurity on neonatal outcomes is widely recognized, but there are still gaps in the standardization of nutritional guidelines, as pointed out by Alexander et al. (2024) when mentioning that organizations such as the American Academy of Pediatrics reinforce the importance of nutritional support for neonates, but without absolute consensus on the best intervention strategies. The standardization of NP can contribute to greater safety and a reduction in errors, and is advocated by guidelines such as ESPGHAN/ESPEN/ESPR/CSPEN and ASPEN (Kriz et al., 2020). However, Senterre et al. (2024) point out that, despite the advantages of multicompartment bags (MCBs) in reducing infections and optimizing working time, individualized NP is still necessary in specific cases.

The lack of evidence on the ideal composition and timing of starting PN in term and late preterm neonates reinforces the need for research in this area. The timing of NP administration should be assessed with caution, as there is still great variability in clinical practice and a lack of consensus on the ideal time to start it (Moon et al., 2022b). The impact of early NP on clinical outcomes is also debated, with conflicting evidence. A subgroup of the PEPaNIC-RCT clinical trial (2018) found worse clinical outcomes in critically ill neonates undergoing early NP, while a Cochrane review (2020) highlighted that the evidence is still limited and of low quality, making it difficult to define precise recommendations (Moon et al., 2022b). Verlinden et al. (2021) reinforce this uncertainty by showing that children between 29 days and 11 months are more vulnerable to negative impacts of early NP on neurocognitive development, such as difficulties in working memory and planning, while neonates ≤28 days and children ≥5 years showed no significant differences in these outcomes.

The implementation of standardized NP, especially with 3CB bags, can be beneficial to optimize patient safety and reduce hospital costs (Kriz et al., 2020; Senterre et al., 2024). However, clinical practices still vary, and international guidelines do not provide definitive recommendations for all clinical situations (Alexander et al., 2024). Given this evidence, Alexander et al. (2024) emphasize the importance of further studies to reduce variability in clinical practice and optimize the use of NP in neonates. Kriz et al. (2020) and Senterre et al. (2024) argue that well-defined protocols, combined with the use of standardized NP, can contribute to patient safety, reducing complications and improving the efficiency of hospital nutrition. On the other hand, the findings of Verlinden et al. (2021) suggest that early PN may be associated with deficits in neurocognitive development in children between 29 days and 11 months, while Moon et al. (2022b) point out that inadequate management of PN may contribute to metabolic complications, such as alterations in homeostasis and the risk of renal dysfunction. Thus, it is essential to develop guidelines based on robust evidence, ensuring better nutritional support for this vulnerable population.

METABOLIC AND LONG-TERM IMPACTS OF PARENTERAL NUTRITION

Parenteral nutrition (PN) has been widely used to meet the nutritional needs of neonates and pediatric patients with severe intestinal impairment. However, its prolonged administration is associated with several metabolic changes that can impact long-term health. According to Hardy et al. (2020), one of the main challenges of PN is the predisposition to liver alterations, including hepatic steatosis and cholestasis, due to the absence of essential nutrients, such as choline and taurine, which are fundamental for lipid metabolism

and liver detoxification. Choline deficiency, in particular, has been implicated in the pathophysiology of NP-associated liver disease, suggesting that supplementation of this nutrient may be essential to prevent metabolic complications.

Another significant impact of long-term PN is related to changes in protein metabolism and nitrogen balance homeostasis. Frazer and Martin (2021) point out that prolonged administration of PN can result in an imbalance between protein synthesis and degradation, favoring catabolism and compromising adequate growth in neonates. This condition can be aggravated by the low availability of methionine and cysteine, essential sulphur amino acids for the synthesis of glutathione and other antioxidant compounds that protect against oxidative stress. The study by Karthigesu, Bertolo and Brown (2021) reinforces that chronic oxidative stress resulting from NP can lead to mitochondrial dysfunction and the progression of metabolic complications.

In addition to liver and protein changes, PN can also interfere with lipid metabolism and neurocognitive development. Rizzo et al. (2022) point out that neonates submitted to PN for prolonged periods show significant changes in lipid profiles, including a reduction in the levels of essential fatty acids and lipoproteins, compromising neuronal myelination and brain development. Similarly, Bernhard et al. (2024) point out that choline deficiency in NP can compromise the synthesis of phosphatidylcholine and sphingomyelin, which are essential for the integrity of cell membranes and neuronal signaling (Bernhard et al., 2024). Thus, supplementation strategies for choline and other essential nutrients should be considered in clinical practice to mitigate the metabolic and long-term impacts of NP

ESSENTIAL NUTRIENT SUPPLEMENTATION IN NP

Parenteral nutrition (PN) is essential for neonates who cannot receive adequate enteral feeding, but its composition needs to be adjusted to ensure an adequate supply of essential nutrients. According to Akour et al. (2024), the deficiency of trace elements such as zinc, selenium and iron is common in patients undergoing PN for long periods, which can negatively impact the immunological and metabolic development of these newborns. Studies suggest that personalized supplementation of these micronutrients is essential to avoid adverse outcomes related to growth and metabolic homeostasis. Quan et al. (2022) reinforce that the addition of iron to PN should be balanced to prevent anemia without aggravating oxidative stress, since premature neonates are more susceptible to oxidative damage due to the immaturity of their antioxidant defenses.

Another critical point in supplementation is the deficiency of fat-soluble and water-soluble vitamins, which is often underestimated in PN. According to Robinson et al. (2023), adequate vitamin D supplementation in PN plays an essential role in bone mineralization, preventing the development of neonatal osteopenia. In addition, vitamin A deficiency is a risk factor for pulmonary complications, since this nutrient is essential for the development of the respiratory epithelium. Pérsico et al. (2023) point out that not adding iodine to PN can lead to thyroid dysfunction, negatively impacting the growth and neurocognitive development of neonates, making periodic monitoring of thyroid hormone levels essential.

The supplementation of essential fatty acids is also a fundamental aspect of neonatal PN. Bernhard et al. (2024) point out that the inclusion of polyunsaturated fatty acids, especially omega-3, in PN can promote brain development and reduce the risk of chronic inflammation, essential factors for

neonatal recovery and growth. Phillips et al. (2022) point out that the implementation of guidelines for the balanced supplementation of macronutrients and micronutrients in PN has resulted in significant improvements in neonatal growth parameters and the prevention of metabolic complications. Moon et al. (2020) add that early administration of amino acids in PN can optimize protein retention and contribute to a better nitrogen balance, reducing complications associated with neonatal malnutrition (Moon et al., 2020).

In addition, protein supplementation and optimizing the composition of energy substrates are crucial elements in PN. According to Trivedi, Jatana and Sinn (2024), the early administration of amino acids can favor a positive nitrogen balance, promoting better growth and neurodevelopment in preterm newborns. Adequate protein and carbohydrate intake, combined with the addition of structured lipids, has been shown to have a positive impact on reducing metabolic complications and supporting adequate growth in critically ill neonates. Thus, individualized and evidence-based strategies for supplementing essential nutrients are fundamental to guaranteeing a better prognosis for neonates undergoing PN.

FINAL CONSIDERATIONS

Parenteral nutrition (PN) plays an essential role in the metabolic and energy support of premature neonates when enteral nutrition is not viable, helping to reduce the risks of malnutrition, impaired growth and damage to the immune system. However, its prolonged use is associated with various complications, including hepatic steatosis, cholestasis, changes in lipid profile, impact on brain development and micronutrient deficiencies. Therefore, the decision to introduce and maintain NP must be made carefully, with an individualized assessment that balances the benefits and risks of this therapeutic approach. There are still gaps in the literature regarding the ideal composition and the most appropriate time for the introduction of PN in neonates, especially term and late preterm infants. Thus, it is essential to carry out future studies that delve deeper into these issues and help formulate evidence-based clinical guidelines, allowing for greater standardization and safety in their application.

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