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PREVENTING BRAIN DAMAGE IN PREMATURE NEWBORNS: CONTROVERSIES AND THERAPIES

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Abstract: Objective: To evaluate the available evidence on preventive strategies and potential therapies for brain injuries in preterm infants, discussing their limitations, controversies and impacts on long-term neurological development. **Methodology:** Narrative bibliographic review carried out on PubMed using the search strategy: (brain injury) AND (preterm infant) AND (therapies). We used 15 articles selected after applying the inclusion and exclusion criteria from 2019 to 2024. **Discussion:** Although postpartum mortality in premature infants has decreased, preterm neonates still face high rates of neurological impairment, such as intraventricular hemorrhage and white matter damage. Recent studies highlight promising therapies, including the use of umbilical cord-derived stem cells, which have the potential to regenerate damaged neural tissue. In addition, erythropoietin (Epo) has been investigated for its neuroprotective properties, such as preventing apoptosis and promoting neurogenesis, and may help with functional recovery after skin injuries. Melatonin, known for its antioxidant and anti-inflammatory properties, is also considered a potential therapy to promote functional recovery after brain injury. However, these approaches still require further clinical validation to be widely innovated in medical practice. **Final considerations:** These therapeutic alternatives, although promising as neuroprotective strategies, lack robust evidence. Currently, only clinical treatment adjustments for infants are widely accepted by consensus. Therefore, further clinical investigation of these studies is crucial so that they can be implemented in practice, considering their great importance in preventing injuries in premature newborns.

Keywords: Brain injury, Premature infants, Treatment, Neuroprotective therapies.

INTRODUCTION

Prematurity is one of the main concerns in the field of neonatology, affecting a significant proportion of births worldwide, with rates varying between 8% and 10%. Premature newborns face high risks of complications, especially brain damage which can result in neurodevelopmental deficits and compromise their long-term quality of life. The fragility of brain development during the first stages of life makes these babies particularly vulnerable to neurological insults, such as hypoxia, systemic inflammation and intensive care practices. Thus, modern neonatal care prioritizes not only survival, but also the promotion of healthy and sustainable neurodevelopment (Lien, 2020).

In addition to representing a clinical challenge, prematurity has significant public health implications, with perinatal brain injury being one of the leading causes of neurological disability in newborns (Singhi; Johnston, 2019). Therapeutic strategies, such as prenatal steroid administration, therapeutic hypothermia and emerging neuroprotective agents, have been explored. However, they still face limitations in terms of efficacy and safety, highlighting the need for evidence-based neonatal practices to mitigate the adverse impacts of prematurity and improve neurodevelopmental outcomes (Van Bel; Vaes; Groenedaal, 2019).

Severe injuries, such as periventricular-intraventricular hemorrhage (PIVH) and white matter injury (WMI), are among the main complications associated with prematurity, often resulting in severe and permanent neurological deficits. Despite advances in neonatal management, strategies to prevent and treat these injuries are still heterogeneous and limited. Recent studies suggest that vascular, hemodynamic and inflammatory immaturity, in addition to the unprotected ex utero environment, play central roles in the cerebral vulnerability of premature newborns (Lien, 2020; Van Bel; Vaes; Groenedaal, 2019).

Another critical area is early diagnosis and continuous monitoring of brain function. Techniques such as near-infrared spectroscopy (NIRS) and amplitude-integrated electroencephalography (aEEG) have shown promise for assessing oxygenation and cortical updating, but are still underutilized in many contexts (Lien, 2020). In addition, interventions such as reducing environmental stressors in the NICU and family-centered care have shown positive impacts on neurodevelopment, but their implementation still lacks clear universal guidelines (Molloy *et al.,* 2023).

The consensus gap in prevention and monitoring strategies highlights the importance of verifying and consolidating the available evidence. Identifying approaches is key to improving neonatal care and promoting more developed advances for preterm newborns (Lien, 2020; Van Bel; Vaes; Groenedaal, 2019).

Perinatal organic injuries are one of the main contributing factors to neurological impairment in newborns, reinforcing the relevance of preventive and therapeutic strategies to minimize sequelae (Singhi; Johnston, 2019). Given this scenario, the aim of this study is to evaluate the available evidence on preventive strategies and potential therapies for specific injuries in preterm newborns, discussing their limitations, controversies and impacts on long-term neurological development.

METHODOLOGY

This is a narrative 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 are the most effective neuroprotective strategies for preventing brain damage in premature newborns, and what are the controversies associated with these interventions?". 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 term "AND", using the following search strategy: (brain injury) AND (preterm infant) AND (therapies). From this search, 256 articles were found, which were then submitted to the selection criteria. The inclusion criteria were: articles in English, published between 2020 and 2024, which addressed the themes proposed for this research, systematic reviews, meta-analyses and randomized clinical trials. 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 inclusion and exclusion criteria, 15 articles were selected from the PubMed database to make up this study's collection.

DISCUSSION

Mortality after premature birth has decreased, but preterm newborns have high rates of neurological impairment. The lower the gestational age and birth weight, the greater the susceptibility to neurological injuries and complications (Yates *et al.,* 2021). Factors such as hypomyelination, low antioxidant capacity and reduced immune surveillance deficits contribute to neuroinflammation in these neonates (Ma; Shi, 2022; Lear *et al.,* 2022). In addition, external conditions such as hypothermia, low oxygen saturation and ventilation with high tidal volumes, associated with systemic alterations such as patent ductus arteriosus, anemia and hypoglycemia, impact cerebral oxygenation levels and increase the risk of injury (Costa; Hakimi; Belo, 2021).

Other factors, such as intrauterine infections, for example chorioamnionitis, further compromise the myelination and maturation of oligodendrocytes, as well as causing dysfunctions in the blood-brain barrier, facilitating the entry of pro-inflammatory mediators (Ophelders *et al.,* 2020). These pathophysiological changes increase the incidence of intraventricular hemorrhage (IVH), which occurs in around 25% of very premature newborns (<32 weeks) and is one of the main causes of morbidity and mortality in neonatology (Wellmann *et al.,* 2022). In severe cases, HVI affects 8% of very preterm infants and more than 16% of preterm infants (<28 weeks) (Razak *et al.*, 2023).

In addition to HVI, white matter damage is predominantly found in premature infants and is related to both hypoxia and perinatal infections and dysfunctions in myelination (Peng *et al.,* 2020; Costa; Hakimi; Bel, 2021). Another relevant condition is hypoxic-ischemic encephalopathy, caused by perinatal asphyxia, which has an incidence of up to 60% in low birth weight and premature newborns, and is one of the main causes of neonatal death (Yang; Zhao; Cui, 2020).

Given the complexity of these conditions, neurocritical care for premature babies requires an integrated approach that takes into account brain immaturity and vulnerability to injury at different stages of development. Interventions such as the use of corticosteroids and magnesium sulphate in prenatal management, as well as delayed umbilical cord clamping, have been shown to be effective in reducing the risk of complications, including skin lesions (Lien, 2020). In the NICU, technologies such as near-infrared spectroscopy (NIRS) and amplitude-integrated electroencephalography (aEEG) play key roles in monitoring cerebral oxygenation and detecting seizures, allowing for early interventions. Neuroimaging tools, such as cranial ultrasound and magnetic resonance imaging, also help in the early identification of lesions and the prediction of neurological outcomes (Parikh; Juul, 2019).

Emerging therapies offer promising alternatives. Stem cells derived from umbilical cord blood (UCB) have neuroprotective,

anti-inflammatory and regenerative properties. Studies highlight advantages such as low immunogenicity, the ability to stimulate neural plasticity, regeneration and angiogenesis. However, issues such as optimal dose, route of administration, time window and long-term effects still need to be clarified in robust clinical trials (Peng *et al.,* 2020; Qiu *et al.,* 2021). Future prospects include combining stem cell therapies and other neuroprotective approaches to improve outcomes in premature neonates (Ophelders *et al.*, 2020).

In addition, magnesium sulfate has been shown to be effective as a neuroprotective agent in women at risk of preterm birth, reducing the incidence of cerebral palsy (CP) by 31% and the risk of motor dysfunction in neonates by 39%. This efficacy is based on its ability to stabilize cell membranes, reduce oxidative stress and secondary symptoms (Parikh; Juul, 2019). Another promising approach is the use of melatonin, which has antioxidant and anti-inflammatory properties. Studies in animal models have demonstrated its neuroprotective efficacy, but further research in neonates is needed to validate its safety and clinical efficacy (Qiu *et al.,* 2021).

Despite recent advances, neuroprotective strategies for preterm newborns still lack robust evidence, especially for extreme preterm infants. The complexity of premature brain damage requires integrated approaches that combine advanced monitoring technologies, emerging therapies with neuroprotective potential and evidence-based clinical interventions (Ma; Shi, 2022). To achieve better results, it is essential to invest in research that deepens understanding of the pathophysiological mechanisms involved, identifies precise therapeutic targets and evaluates the efficacy and safety of new strategies. Only through collaborative efforts between multidisciplinary teams will it be possible to optimize management, improve quality of life and ensure healthy neurodevelopment for these vulnerable neonates (Peng *et al.,* 2020).

FINAL CONSIDERATIONS

Although postpartum mortality in premature infants has decreased in recent years, preterm neonates still face a high risk of neurological impairment, such as intraventricular hemorrhage and white matter damage, which can result in severe sequelae, including cerebral palsy and cognitive deficits. Conditional preventive strategies, such as the use of corticosteroids and magnesium sulphate prenatally, delayed clamping of the umbilical cord and neurocritical management in the NICU, with strict control of circulatory homeostasis, continuous monitoring of cerebral oxygenation by near-infrared spectroscopy (NIRS), integrated amplitude EEG and advanced neuroimaging, bring significant benefits. Meanwhile, promising advances are emerging, such as therapies with stem cells derived from umbilical cord blood, which have the potential for immune modulation and neural regeneration, and neuroprotective agents such as melatonin, recognized for its antioxidant and anti-inflammatory properties, and erythropoietin, which stimulates neurogenesis and reduces apoptosis. Despite the potential of these approaches, they still lack robust evidence for large-scale clinical implementation, making it essential to carry out larger, well-structured future studies that validate their efficacy and safety, enabling more effective interventions to prevent and treat neurological injuries in premature newborns.

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