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FUTURE OF NEUROPROTECTIVE THERAPIES IN THE NICU FOR PREMATURE INFANTS: A SUMMARY

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ABSTRACT

Moderate to severe neuro-developmental delays, behavioral problems, and mental health disorders are more common in premature infants, and they can have a lasting detrimental effect on their quality of life. Furthermore, babies that are born with a super low weight, less than 1000g, are more likely to have long-term problems that will cost more in the long run. Consequently, it is more effective to involve parents at an early stage so that they can create a setting that is both neuroprotective and developmentally beneficial for their baby. Studies have primarily shown short-term benefits for prenatal steroid therapy, but minimal effect of these therapies on long time for the development of neuronal development. Despite this, magnesium and antenatal steroids have become conventional medications for preterm new-borns. Developing better neuromonitoring technologies to optimize trial recruitment, more accurate biomarkers to measure treatment response, and more effective neuroprotective and neurorestorative medicines is critical.

KEYWORDS: Premature infants, Neuroprotective therapies.

INTRODUCTION

Although the mortality rate of infants, particularly premature infants, has significantly decreased in recent times, while, the rate of morbidity is not as improved. In addition, whereas the occurrence of newborn encephalopathy in full-term children has remained largely stable in affluent countries, the rates of premature deliveries in the same context are continuously rising (1). Therefore, addressing therapies for neurocognitive morbidity is crucial. However, the present intervention options are restricted in their effectiveness, although new medications are showing significant potential (2).

Perinatal brain injury refers to injuries that result from complex, multiple factors and can vary in severity across individuals. It affects infants with varied genetic origins and can occur at different phases of their physiological development (1,3). There is currently substantial data indicating that the development of brain injury in preterm infants is caused by multiple factors. These factors include hypoxia-ischemia (HI), exposure to infection or inflammation during the perinatal period, the use of ventilation and other technology to sustain immature infants, as well as other events occurring around the time of birth (2,4).

Periventricular leucomalacia is more common in premature infants, but hypoxic-ischemic encephalopathy is mostly diagnosed in full-term infants. Diffuse white matter damage, and poor myelination is the most prevalent underlying disease in contemporary cohorts (5). Cerebral palsy is characterized by widespread damage to the white matter of the brain, with the most severe cases involving the formation of cysts. This condition was previously referred to as cystic periventricular leukomalacia3. Empirically, a significant reduction in the number of cells typically happened within the initial days following an injury, coinciding with a subsequent decline in brain oxidative metabolism. Interestingly, in several trials, it was seen that harm persisted and developed further over days and weeks, known as the tertiary phase of injury (6-7).

To create new neuroprotective techniques, it is essential to have a comprehensive understanding of the pathophysiology of each condition. This understanding will help identify specific indicators or targets/pathways that may be used to assess the effectiveness of potential compounds. Furthermore, as developmental processes are susceptible to injury and therapy, it is crucial to carefully consider both the immediate and prolonged harmful effects.

Neuroprotective Strategies

Neuroprotective approaches typically involve inhibiting sensitizing factors, preconditioning against damage, pharmacologically blocking mechanisms involved in damage, or promoting endogenous reparative processes or inducing reparative processes themselves. Therapies are effective in reducing the diameters of lesions and their associated consequences, and the most effective among them target numerous pathophysiological pathways. Although medications frequently exert their effects on multiple stages of a harm cascade (6,8).

Antenatal steroids

Premature neonates who are given corticosteroids throughout pregnancy have better neurodevelopmental outcomes and experience considerable short-term benefits. Accelerating embryonic lung growth and stabilizing the fetal neurovasculature are the main goals (9). The risk of perinatal death and the risk of neonatal death and respiratory distress syndrome are both reduced by prenatal corticosteroid treatment, according to a recent meta-analysis. Additionally, they likely lessen the likelihood of IVH (RR 0.58, 95% CI 0.45 to 0.75) and childhood developmental delay (RR 0.51, 95% CI 0.27 to 0.97) (10-11). The use of these in infants who are moderately to late preterm is fraught with controversy, though, because the hazards may exceed the benefits and the potential for benefit is substantially reduced in this population.

Magnesium sulfate

Antenatal administration of magnesium sulfate (MgSO4) before preterm birth to protect the embryonic nervous system is commonly practiced. This approach is supported by the analysis of many trials involving 6131 newborns, which includes a recent study that analyzed individual participant data. Magnesium forms a bond with NMDA receptors and prevents them from being activated; this inhibition is reversed when the cell membrane becomes depolarized (12-13). Thus, magnesium plays a regulatory role and prevents excessive excitotoxic stress. An animal model has shown an effect that prevents programmed cell death (14). Administering magnesium to pregnant women at risk of premature delivery has been found to have a positive effect on reducing the occurrence of cerebral palsy and motor impairment in premature infants.

Topiramate

AMPA and kainate receptor antagonists, such as topiramate, have not been shown to harm neuronal survival as much as NMDA receptor antagonists in the brain during development. Topiramate also protects preoligodendrocytes, which are severely damaged by excitotoxic or hypoxic-ischemic stress in neonates. The antiepileptic treatment is licensed for two-year-olds due to its protective impact (15-16).

Allopurinol

Allopurinol inhibits xanthine oxidase. Its neuroprotective impact comes from lowering oxidative damage and cerebral edema. Multiple animal models have shown its good tolerability, paving the way for human clinical studies. It has been tested on hypoxic-ischemic encephalopathy babies (17-18). The first trial found that allopurinol reduced NO levels in neonates with intermediate to severe hypoxic-ischemic encephalopathy between 72 and 96 hours after birth.

Erythropoietin

Erythropoietin (EPO) is a cytokine that promotes hematopoiesis by stimulating the proliferation and differentiation of erythroid progenitor cells. It is secreted in response to hypoxia, or low oxygen tension. Moreover, it is a ubiquitously expressed signaling protein that possesses receptors on cells inside the central nervous system (19). Moreover, the recombinant variant of erythropoietin (rEPO) is presently employed in neonatal medicine for the treatment of prematurity-related anemia. Moreover, experimental animal models have been utilized to examine its effects on brain damage during the developmental stage. Empirical evidence has demonstrated a decline in proinflammatory cytokines, oxidative stress, and an elevation in trophic factors associated with regenerative mechanisms (20). Furthermore, there is a documented antiapoptotic effect and a reestablishment of the energy level. A comprehensive clinical trial conducted on premature neonates has shown a significant benefit in terms of early brain imaging.

Pluripotential (stem) cells

Diffuse white matter injury (WMI) is a hallmark of neurodevelopmental dysfunction following premature birth, according to new data from contemporary cohorts. This condition is a reflection of white matter maturation that is consistently disrupted. Some important factors include inflammation and the ongoing loss of trophic support (21). The use of exogenous pluripotent stem cells (stem cells) can enhance outcomes following preterm brain injury by promoting angiogenesis, neurogenesis, synaptogenesis, and neurite outgrowth. However, its usage to this point has been mostly in a preclinical

setting (4). The best way to administer the treatment, which stem cells to use, and when to begin treatment are just a few of the many unanswered concern.

Stem Cell Treatment

Now that a reliable method for cultivating and using stem cells has been developed, the possibility of using these cells to repair brain injuries can be considered. The exact mechanism by which stem cell therapy improves lesion size, extent, and prognosis after brain lesions remains unclear, however some studies have found a favorable effect (22). This could be due to substances produced by stem cells or to the stem cells themselves. The stem cells must divide, locate the injury, and then differentiate into a suitable cell type (e.g., neuron, oligodendrocyte) before they can integrate into the tissue and have any kind of effect. Mesenchymal stem cells derived from cord blood or induced pluripotent stem cells (iPS) present less of an ethical dilemma than other human stem cell types (23). With these cells, an autologous transplant can be performed without worrying about the immune system developing resistance to the new cells. Children who have suffered perinatal brain injuries are the subjects of multiple ongoing therapeutic trials that use stem cells obtained from cord blood.

Bundles targeting neuroprotection and neuroplasticity

A multitude of factors contribute to the complexity of preterm brain damage. The risk of, response to, or severity of new-born brain injury depends on a complex interplay of prenatal, perinatal, postnatal, genetic, epigenetic, metabolic, and other factors. A "bundled" strategy utilizing quality improvement methods is gaining popularity as a means to avoid acute preterm brain injury, despite the issue's complexity (24). There are two types of neuroprotection bundles: those that aim to prevent acute brain injury and those that target neuroplasticity. Prevention bundles for preterm acute brain injury focus on several important areas, including the following: the early identification of pregnancies at high risk and the transfer of the fetus inside the womb; the prevention of acidosis; the positioning of the head in the centre; the minimization of painful medical operations; and the regulation of electrolyte levels, including serum sodium. Recent research shown that neuroprotection bundles using Quality Improvement methods reduced immediate brain injury and improved long-term neurodevelopment in extremely preterm infants born at and outside of tertiary facilities. The bundles could target those crucial ingredients (8, 25).

CONCLUSION

Although survival rates have improved, preterm delivery still causes a heavy load of lifetime issues. The diverse causes of preterm brain injury make it difficult to develop effective treatments. These causes include exposure to hypoxia during pregnancy and after birth, acute perinatal asphyxia, infection or inflammation during pregnancy or after birth, ventilation-induced brain injury, and the potential side effects of medications like glucocorticoids and anticonvulsants. Despite the success of hypothermia and magnesium sulfate, their use in humans is still limited. Neuroprotective techniques also require a global systematization of clinical trials.

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