Current Research in Neonatal Hypoxic-Ischemic Anti-Inflammatory Therapeutics

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Abstract

A number of studies have reported that inflammation is critical in the evolution of neonatal encephalopathy, evidencing that there is a strong association between perinatal hypoxia-ischemia, the secondary inflammatory response to the insult and persisting neurodisability in survivors. Despite this process can be necessary to remove cell debris and to start regenerative processes, it can become one of the leading pathogenic factors of neonatal brain damage. In the present review we focus on the current ongoing clinical trials on neonatal hypoxic-ischemic encephalopathy that are using anti-inflammatory compounds.

Keywords: Neonatal Encephalopathy; Perinatal Hypoxia-Ischemia; Brain Injury; Inflammation; Therapeutics; Clinical Trials

Introduction

Following perinatal hypoxia-ischemia, a bidirectional communication exists between the injured brain and peripheral innate and adaptive immune system, which can in turn modulate the progression of ischemic pathology. After the onset of the injury, brain cells release pro-inflammatory cytokines and chemokines that induce the recruitment of white blood cells [1]. The infiltration of macrophages can be both protective against hemorrhage and necessary to remove cell debris but can also be detrimental in ischemic injury, impairing tissue repair. Together with an increase in the concentration of reactive oxygen species [2] leading to oxidative stress by lipid peroxidation, both infiltrating cells from blood capillaries and microglia can continue secreting a number of inflammatory mediators that can exacerbate the damage [1]. These factors can include a wide range of molecules, being the most recognized the inflammatory cytokines tumor necrosis alpha, interleukins-1-beta, -9 and -18, chemokines like macrophage inflammatory protein-1 and macrophage chemoattractant protein-1, nitric oxide and matrix metalloproteinases [1] which have been shown to be related with delayed cell death and brain injury [2].

This inflammatory response normally starts a few minutes/hours after the onset of the injury and can extend even for months to years, in a late phase of damage known as tertiary brain injury. This process can block neuroreparatory processes and affect brain development, leading to long-term neurological sequelae such as cerebral palsy and epilepsy and also to attention deficits and hyperactivity in children and adolescents [1]. Together, these data emphasize the significant contribution of infection/inflammation in the developing brain contributing to neonatal encephalopathy.

To date, therapeutic hypothermia is the only current standard clinical care for neonatal encephalopathy in high income settings. There is clear evidence that in intensive care settings therapeutic hypothermia reduces adverse outcome (mortality and neurodevelopmental disability) at 18 months of age (typical relative risk 0.75%, 95% CI 0.68 - 0.83) [3]. However, it offers a discrete reduction of 11% in risk of death or disability [4] and approximately 40% of infants have an adverse neurodevelopmental outcome despite hypothermic treatment [5].

In order to reduce the undesirable consequences triggered by neonatal brain injury-induced inflammation, the use of anti-inflammatory medicines has been extensively studied and can be considered as another meaningful tool against hypoxic-ischemic brain injury. These pre-clinical studies have evaluated the therapeutic capacity of antioxidant protective medicines like hydrocortisone, melatonin, endo-cannabinoids or erythropoietin. Indeed, recent data suggest that cooling may be less effective in the presence of infection/inflammation (6-8). In a clinical study evaluating how induced hypothermia could ameliorate the brain injury induced by asphyxia, the principal glucocorticoid secreted by the adrenal gland, hydrocortisone (NCT02700828), was evaluated in a phase II clinical trial. The study aimed to determine the safety and feasibility of using hydrocortisone in neonates with hypothermia, and the results showed that hydrocortisone was well-tolerated and safe. Furthermore, a recent study (9-12) published in the Journal of Pediatrics evaluated the therapeutic capacity of antioxidant protective medicines like hydrocortisone, melatonin, endo-cannabinoids or erythropoietin.
Conclusion

In an effort to improve the clinical course of neonatal brain injury, a number of clinical studies are underway to determine optimal treatments using anti-inflammatory drugs. Further studies are needed to determine the optimal dose and interval of administration of every single compound tested. The use of synergic strategies, such as the association between hypothermia and some of these anti-inflammatory treatments, may lead to a larger neuroprotective effect on the brain thus improving the neonatal outcome.

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Conflict of Interest

The authors declare no conflict of interest.

Bibliography


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