Newer Therapies In Management of Neonatal Birth Asphyxia

Prof. Dr. Sunil Natha Mhaske[1], Dr. Abhijit Shinde[2], Dr. Sushrut Kumar[2]

[1]Dean & Professor, [2]Assistant Professor, Department of Paediatrics, DVVPF's Medical College & Hospital, Ahmednagar-414111, Maharashtra, India

Corresponding Author: Dr. Abhijit Shinde

Email ID: jeetshinde007@gmail.com

Address: Department of Paediatrics, DVVPF's Medical College & Hospital, Ahmednagar-414111, Maharashtra, India

Abstract :

Asphyxia is an insult to the fetus or newborn due to lack of oxygen or lack of perfusion to various organs.[1] National Neonatology Forum of India has defined asphyxia as gasping or ineffective breathing or lack of breathing at 1 min of life.[2] Birth asphyxia is one of the most important causes of neonatal brain injury whose incidence ranges from 3.7 to 9/1000 deliveries in the west.[3] With the advent of therapeutic hypothermia (TH), improved outcomes are being reported in moderate HIE. TH, however, has not demonstrated improvement in outcomes related to severe HIE. . This has led clinicians and researchers to continue evaluating complementary and/or alternative therapies for infants with HIE. In this review, we will discuss current and emerging therapies in the management of HIE, other than hypothermia. With issues of access to health care and the burden of birth asphyxia shifting to developing and least developed nations, there is a need for alternative and supplementary neuroprotective agents. Low cost and easy availability along with ease of use would assist in ensuring that these therapies have global applicability. So global efforts must be taken to increase such studies as birth asphyxia is causing more morbidity & mortality globally.

Key words: Birth asphyxia, Neonatal Hypoxia, Neonatal encephalopathy, Therapeutic hypothermia

Introduction:

Asphyxia is an insult to the fetus or newborn due to lack of oxygen or lack of perfusion to various organs.[1] National Neonatology Forum of India has defined asphyxia as gasping or ineffective breathing or lack of breathing at 1 min of life.[2] Birth asphyxia is one of the most important causes of neonatal brain injury whose incidence ranges from 3.7 to 9/1000 deliveries in the west.[3] In addition to its contribution to mortality, birth asphyxia can result in cognitive impairment, epilepsy, cerebral palsy, and chronic disease in later life.[1,4-7] Birth asphyxia is the third largest (16%) reason for neonatal mortality and morbidity after prematurity (32%) and septicemia (19%).[8-11]

About 0.75 million neonates die every year in India, the highest for any country in the world. The neonatal mortality rate (NMR) declined from 52/1000 live births in 1990 to 28/1000 live births in 2013, but the rate of decline has been slow.

Obviously, the "Committing to Child Survival: A Promise Renewed" goal of reducing under-five mortality to 20 or less per 1000 live births by 2035 will not be attained without specific efforts to reduce newborn mortality.[10] This study is an effort to study and analyze the risk factors leading to birth asphyxia in peripheral areas.

The most common contributor to early neonatal mortality is birth asphyxia with prematurity, infections, and low birth weight being other major contributors. Four million newborn infants experience birth asphyxia each year, accounting for an estimated one million deaths and 42 million disability-adjusted life years.[12] Many of these infants sustain significant brain injury and develop long-term sequelae, most commonly cerebral palsy, epilepsy, and sensory deficits.[12] Advances in managing infants with birth asphyxia, leading to hypoxic ischemic encephalopathy (HIE) on a global scale will contribute significantly to achieving the 2030 sustainable developmental goals.

With the advent of therapeutic hypothermia (TH), improved outcomes are being reported in moderate HIE. TH, however, has not demonstrated improvement in outcomes related to severe HIE. As hypothermia, both whole body and head cooling, is being evaluated and used across the globe, several limitations for its use, related to accessibility, provision of adequate facilities for initiation and monitoring hypothermia and financial limitations—especially in India—are being recognized.

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This has led clinicians and researchers to continue evaluating complementary and/or alternative therapies for infants with HIE. In this review, we will discuss current and emerging therapies in the management of HIE, other than hypothermia.

Current scenario for treatment of birth asphyxia:

Any pregnancy that is identified as being at high risk for neonatal complications should ideally be delivered at a tertiary care center with trained and experienced resuscitators. Management of an infant who is depressed at birth involves following accepted guidelines such as those published by ILCOR and Neonatal Resuscitation Program.[13] The infant is evaluated for hypothermia, which should ideally commence within 6 h of birth for infants with moderate to severe HIE.[14] Improved motor outcomes have been noted with earlier cooling within 3 h after birth.[15] Supportive management of seizures, fluid balance, and hematological and cardiovascular abnormities is essential in ensuring optimal outcomes.[16] Presence of a multidisciplinary team including pediatric neurologists, cardiologists, and other subspecialties as well as institutional capabilities for long term EEG, MRI, and physical and occupational therapies are a requisite for establishment of a cooling protocol at tertiary institutes.[16] Follow up with a developmental pediatrician and enrollment in Early interventional programs are also essential to optimize outcomes for infants with HIE.[17]

Newer Treatment Alternatives for Birth Asphyxia

Most of the neuroprotective strategies being evaluated for use in management of HIE, are primarily to mitigate the devastating effects from secondary energy failure on the brain. Therapies that are applied in experimental and animal models of HIE generally work on slowing the pathophysiology that include decreasing oxidative stress, antagonizing excitatory neurotransmitter release or receptor blockade, anti-inflammatory effects, immunomodulation or by decreasing apoptosis among others. While some are undergoing randomized controlled trials such as erythropoietin and its analogues, others are being researched in experimental animal models.

1. Resuscitation

A. Optimizing Placental Transfusion

Either by delayed cord clamping (DCC) or by the process or cord milking/stripping may impart a neuroprotective effect, besides improving hemodynamics.[18] Full-term infants who underwent DCC had a 45% higher mean ferritin concentration at four months of age[19], demonstrating a beneficial effect in preventing iron deficiency anemia. Iron plays an important role in brain myelination[20], suggesting a neuroprotective effect of placental transfusion. Additionally, umbilical cord derived stem cells are being evaluated for treatment of HIE, and ensuring an optimal placental transfusion ensures that the compromised infant receives the entire complement of stem cells.

B. Vasopressin

Use of vasopressin as an alternative to epinephrine in neonatal resuscitation is being evaluated in pre-clinical studies. This medication has a neuroprotective potential as studies in rat and guinea pig have demonstrated that vasopressin activates hippocampal interneurons, silencing synchronous neuronal activity.[21] This may reduce neuronal energy demand, which could be a neuroprotective mechanism.

2. Erythropietin/Analogues (Endogenous)

Erythopoietin (Epo) is an endogenous protein, synthesized in the fetal liver that has an impact on multiple critical pathways. Besides stimulating erythropoiesis, Epo is a cytokine that influences the body's immune response.[22] Additionally, its neuroprotective role has been recognized and evaluated in pre-clinical and clinical studies. Epo receptors (EpoR) are widely expressed throughout the central nervous system in several cell types including progenitor cells, astrocytes, oligodendrocytes, and microglia[23,24], to name a few. Epo and EpoR are upregulated following hypoxic ischemic injury and Epo has an anti-oxidant[25] as well as anti-inflammatory effect. It reduced apoptotic and excitotoxic cell injury. Clinical trials evaluating Epo alone in infants with HIE have shown promising results. Since hypothermia has become standard of care therapy for HIE, larger trials are currently on going evaluating Epo as a complement to cooling therapy. A Phase I trial evaluating effective dose and safety demonstrated that a moderately high dose of 1000 U/kg achieved levels (based on animal studies) that would protective maximal neuroprotection and minimize risks of excessive Epo. In a Phase II double-blinded, placebo-controlled trial in infants undergoing TH for HIE, multiple doses of Epo (1000 U/kg) resulted in less MRI brain injury and potential for improved short-term motor outcomes.[26]

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3. Stem Cells

Recent experimental studies in animal models have indicated that various mechanisms of action are involved in the process by which umbilical cord blood cells (UCBCs) protect the brain from hypoxic ischemic injury. These stem cells are predominantly derived from two sources—bone marrow derived mesenchymal stem cells (BM-MSC) and umbilical cord blood derived mesenchymal stem cells (UCB-MSC).[27]

4. Remote Ischemic Postconditioning (Endogenous)

The concept of remote ischemic conditioning (RIPC) involves delivery of sub-lethal small ischemic insults, remote from the area of injury, that activate endogenous repair pathways which potentially help in reducing the extent of original ischemic injury. This has previously been studied in adult cardiac injury[28], however is now being evaluated both in adult and neonatal brain ischemia and stroke.

5. Endocannabinoids (Endogenous)

The endocannabinoid system has been recognized as an important neuroregulatory mechanism that could help in protection from brain injury. Activation of this system has been shown to decrease glutamate excitotoxicity and activation of microglia and cell death pathways. Use of a cannabinoid (CBD) receptor 1 and 2 (CBR1 and CBR2) agonist WIN 55212-2 in a rodent model of neonatal HIE demonstrated protective effects by prevention of glutamate release, TNF alpha accumulation, and iNOS induction, resulting in decreased cell death.[29]

6. Melantoin

Melatonin is an endogenous neuroendocrine moiety secreted by the pineal gland and well known for its role in modulating the circadian rhythm. Besides this, melatonin has several other mechanisms that suggest an important role in recovery and repair from brain injury. Melatonin plays an important role in normal glial development and has anti-apoptotic , anti-inflammatory, and anti-oxidant effects.[30]

7. Monosialoganglioside

Gangliosides are sphingolipids that serve an important function in maintaining cell membrane integrity. In a rat model of neonatal hypoxic ischemic injury, reduced ganglioside, phospholipid, and cholesterol contents in the hippocampus were noted.[31]

8. Xenon

Acute hypoxic ischemic insult leads to NMDA receptor activation through neuronal depolarization. Xenon inhibits NMDA signaling and thus may play a role in reducing the acute cell injury. While studies in the piglet model of birth asphyxia suggest a benefit to the combined modality of treatment with hypothermia and xenon.[32]

9. Argon

This is another significantly less expensive noble gas, that has demonstrated significant neuroprotection in animal models of HIE. In an extensive piglet model of ischemic injury, Broad et al. showed augmentation of hypothermic neuroprotection with argon use.[33]

10. Allopurinol

Oxidant injury by free radicals and superoxides formed through activation of the xanthine oxidase pathway contribute to the damage caused by a hypoxic ischemic insult. Allopurinol is a xanthine oxidase inhibitor that is being investigated as a potential agent for use in treatment of HIE. Preclinical studies in various rodent and mammalian models of HIE have shown neuroprotective effects with use alone and recently, as a complement to TH.[34]

11. Magnesium Sulfate

Magnesium sulfate is an NMDA receptor antagonist believed to reduce excitotoxic damage after a hypoxic ischemic insult. It is now being widely used antenatally for neuroprotection in preterm deliveries. Initial interest in use of this medication was generated due to low magnesium levels being noted in infants with HIE.[35]

12. Topiramate

Topiramate blocks the voltage-dependent sodium and calcium channels and also inhibits the excitatory glutamate pathway while enhancing the inhibitory effects of gamma-aminobutyric acid (GABA). All these effects would work favorably in the pathophysiology of HIE. In newborns, it has been extensively studied in the management of HIE in combination with hypothermia. The short-term and safety data support its use in combination with hypothermia in exploring the possible neuroprotective effects.[36]

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13. Azithromycin

Preclinical studies in models of ischemic stroke have revealed that azithromycin has a neuroprotective effect . Recent abstracts have investigated the possibility of using azithromycin in neonatal HIE alone and as an adjunct to hypothermia.[37]

14. Combination Therapies

With the discovery of more therapeutic targets for management of HIE, there is potential for combination and adjunctive therapies with agents that may affect the pathophysiological process at different phases. Additionally, TH is being explored for mild HIE, as neurological deficits have been noted in these infants as well.[38] Melatonin, epo, darbepoetin (it has comparable biological activity to erythropoietin), xenon, and topiramate are all being studied as adjuncts to TH.

Conclusion:

Birth asphyxia contributes to a significantly higher burden of neonatal mortality and morbidity globally, more so in developing countries. Neonatal HIE, apart from increased mortality leads to devastating neurological consequences such as cerebral palsy, epilepsy, and mental retardation. With the advent and widespread clinical use of TH over the last decade, the prognosis of moderate HIE has significantly improved. With issues of access to health care and the burden of birth asphyxia shifting to developing and least developed nations, there is a need for alternative and supplementary neuroprotective agents. Low cost and easy availability along with ease of use would assist in ensuring that these therapies have global applicability.

Several treatment modalities have been explained in this review. But many of them require more randomized contol trials & studies. So global efforts must be taken to increase such studies as birth asphyxia is causing more morbidity & mortality globally.

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