REVIEW ARTICLE

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Therapeutic hypothermia as a form of neonatal hypoxic-ischemic encephalopathy neuroprotection and novel therapeutic options

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Abstract

Introduction and Objective. Hypoxic-ischemic encephalopathy is one of the main types of neonatal encephalopathy in which perinatal asphyxia has been proven. The incidence of neonatal hypoxic-ischemic encephalopathy is estimated at 1–8 per 1,000 newborns and is associated with a variety of long-term complications. The study presents standard and novel treatment pathways and their limitations.

Review Methods. A literature search was performed in the PubMed and Google Scholar databases using the following phrases 'hypoxic-ischemic encephalopathy', 'therapeutic hypothermia', and 'novel treatment'. The research studies used in the review were published between 2019 – 2025.

Brief description of the state of knowledge. A thorough understanding of the pathogenesis of hypoxic-ischemic encephalopathy and neuroplastic features of the neonatal brain has allowed for the singling-out of therapeutic hypothermia as a standard procedure making it possible to significantly reduce mortality and improve the quality of life. However, the condition affects low-income countries even more frequently and, despite treatment, there is a 22% of severe complications or death. Current research focuses on new treatments options like therapeutic hypothermia modifications, such as selective head cooling, whole-body cooling, as well as pharmacotherapy with erythropoietin, stem cells, allopurinol, caffeine, melatonin, endocannabinoids, colony stimulating factors, metformin and more.

Summary. Numerous limitations of therapeutic hypothermia necessitate further investigation. Another promising strategy may be a modification of therapeutic hypothermia and combination therapy.

Key words

encephalopathy, therapeutic hypothermia, hypoxic-ischemic

INTRODUCTION AND OBJECTIVE

Neonatal encephalopathy is defined as a clinical syndrome with symptoms of abnormal neurological function, characterized by difficulties in maintaining respiration, reduced activity, decreased levels of consciousness, reduced muscle tone, persistence of primitive reflexes, and seizures in newborns and pre-term infants [1]. Hypoxic-ischemic encephalopathy (HIE), which arises as a result of reduced oxygen supply and sudden decrease in glucose transport to the brain during the prenatal and perinatal periods, is one of the main forms of neonatal encephalopathy [1, 2].

Factors such as preeclampsia, umbilical cord knot, umbilical cord prolapse, chronic maternal hypoxia, shoulder dystocia, and placental abruption can restrict the flow of oxygenated blood to the brain, leading to cellular and systemic damage [3,4]. The extent of brain damage depends on the duration and onset of hypoxia [4]. According to epidemiological data, HIE affects 1 – 8 newborns per 1,000 live births; this number is higher in low-income countries, reaching up to 26 per 1,000 live births [5]. A strong correlation exists between the occurrence of encephalopathy and gestational age. Among preterm newborns, particularly those born before 28 weeks of gestation, the incidence ranges from 4–48 cases per 1,000 pregnancies, increasing with decreasing gestational age [6]. Mortality rates range from 10% in moderate encephalopathy to 60% in severe cases [7].

The severity of neonatal encephalopathy, the primary cause of which is brain tissue damage, has a close correlation with neurological development outcomes. Infants who survive HIE without motor deficits or with mild HIE may achieve good early childhood outcomes, while those with severe encephalopathy often face a high risk of significant neurological developmental delays. Furthermore, even infants with mild HIE and no motor impairments are more likely to experience subtle cognitive deficits later in life [1, 8]. If left untreated, 62% of infants with perinatal brain hypoxia will die or experience moderate to severe disability by 18–22 months. Treatment reduces this rate to 22%. Among survivors, various neurological complications arise: 45% have cognitive and developmental delays or learning difficulties, 29% are treated for cerebral palsy, 26% have visual impairments, including blindness, 17% face gross motor and coordination problems, epilepsy, 9% experience hearing issues, and 1% have behavioural disorders [1, 7, 9].

Continuous monitoring and assessment at different developmental stages are crucial because normal neurodevelopmental outcomes at 18–24 months post-HIE do not preclude subtle cognitive or behavioural difficulties during school years [1].

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Pathophysiology of hypoxic-ischemic encephalopathy (HIE). The pathogenesis of HIE involves five main processes that take place within the brain: mitochondrial dysfunction, oxidative stress, intracellular calcium accumulation, excitotoxicity, and inflammation [3, 5, 10, 11]. Following an ischemic episode, an acute phase – also known as 'primary energy failure' – occurs. A sudden decrease in the availability of blood and oxygen in the brain has consequences – oxygen is the terminal electron acceptor in the respiratory chain, and its reduced partial pressure causes disruption of oxidative phosphorylation which, in turn, reduces the production of adenosine triphosphate (ATP), the deficiency of which leads to Na+/K+ pump failure and a switch to anaerobic metabolism. Moreover, this phase is characterized by oxidative stress, neuronal death and excitotoxicity. Excitotoxicity results from excessive glutamate release, which over-stimulates 2-(aminomethyl)phenylacetic acid (AMPA), kainate (KA), and N-methyl-D-aspartate (NMDA) receptors. Over-activation of AMPA and KA receptors causes an influx of sodium (Na^+) and chloride (Cl^-) ions, leading to increased cellular osmolality. Meanwhile, NMDA receptor stimulation results in calcium (Ca^{2+}) influx [3, 5, 7, 10]. Calcium-dependent enzymes, such as kinases involved in intracellular signal transduction pathways and dehydrogenases participating in the Krebs cycle, are activated by an increase in the calcium ion concentration. Moreover, an activation of nitric oxide synthase (NOS) is observed leading to an increased formation of reactive nitrogen species which are responsible for mitochondrial damage.

Reactive oxygen species (ROS) over-production causes an increased release of p53 and cytochrome c, as well as activation of caspase-9 and caspase-3, resulting in ROS-induced apoptosis [10, 12, 13]. Additionally, the mitogen-activated protein kinase (MAPK) signalling pathway becomes excessively activated after hypoxic-ischemic episodes, further promoting neuronal apoptosis [3, 5, 7, 10]. Prostanoids also play a role in these processes; appropriate activation can exert neuroprotective effects and prevent neuronal damage in the cerebellum, among other things through cerebral vasodilation mediated by MAPK.

Depending on the duration of ischemia and the initiation of medical interventions, partial functional recovery through reperfusion can occur within 30–60 minutes after a hypoxic-ischemic event [5, 7]. The latent phase follows the acute phase and lasts from 1–6 hours. In moderate to severe HIE, the latent phase progresses into the secondary phase, also known as 'secondary energy failure', ranging from 6–15 hours. The last one is the tertiary phase that develops weeks or months after the initial energy failure [3, 5, 11]. Brain injury during the tertiary phase progresses over months or even years, leading to reduced plasticity and further neuronal loss [11]. Figure 1 displays cellular changes in the brain at different stages of HIE injury.

REVIEW METHODS

The review was conducted using Pubmed and Google Scholar databases searching key words: 'hypoxic-ischemic encephalopathy', 'novel treatment', 'therapeutic hypothermia', and 'pharmacotherapy'. The review was written on the basis of 49 publications from 2019–2025, with special emphasis on the last 4 years.

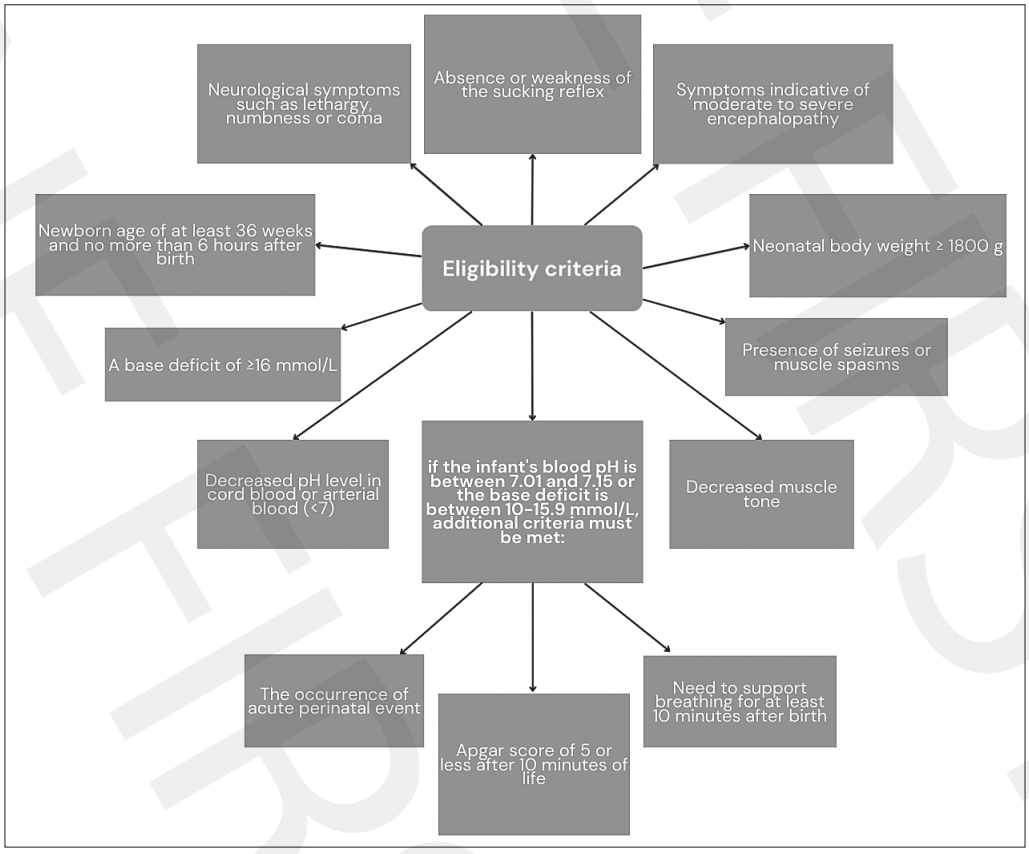

Figure 1. Scheme representing the stages of tissue changes during brain asphyxia [3, 5, 7, 10, 11]

STATE OF KNOWLEDGE

Nowadays, therapeutic hypothermia (TH) is the standard of care for moderate to severe HIE, although its use is limited to the initial phase of encephalopathy treatment. According to current guidelines, the therapeutic window is within six hours after birth, during the latent phase [2, 14]. TH causes a decrease in metabolism and prevents the accumulation of calcium in cells, which prevents neuronal damage. Hypothermia also reduces the production of ROS and inhibits pro-inflammatory pathways by diminishing the production of inflammatory response mediators. Lowering body temperature contributes to a decrease in intracranial pressure and preserves microcirculation. Myocardial metabolism and oxygen demand are also reduced [15]. Despite its undeniable advantages, the therapy is not free of side-effects among which electrolyte disorders, cardiodepressive effects, disruption of surfactant production, deterioration of the oxygenation level of the body, coagulopathy, increased risk of sepsis, intolerance of enteral feeding, pulmonary hypertension, have been noted.

Before initiating TH, arterial blood gasometry should be performed. Electrolytes, coagulation parameters and glucose levels should be measured, renal and liver function should be assessed. When performing TH, ongoing monitoring of vital functions is necessary – blood gasometry every four hours, blood pressure, heart rate and perfusion, as well as mean arterial pressure, pupil response, level of consciousness, skin condition, electroencephalography, echocardiography scan and magnetic resonance imaging (MRI) should be considered to avoid potential complications [2, 16]. Moreover, it is mandatory to meet a range of inclusion criteria (Fig. 2).

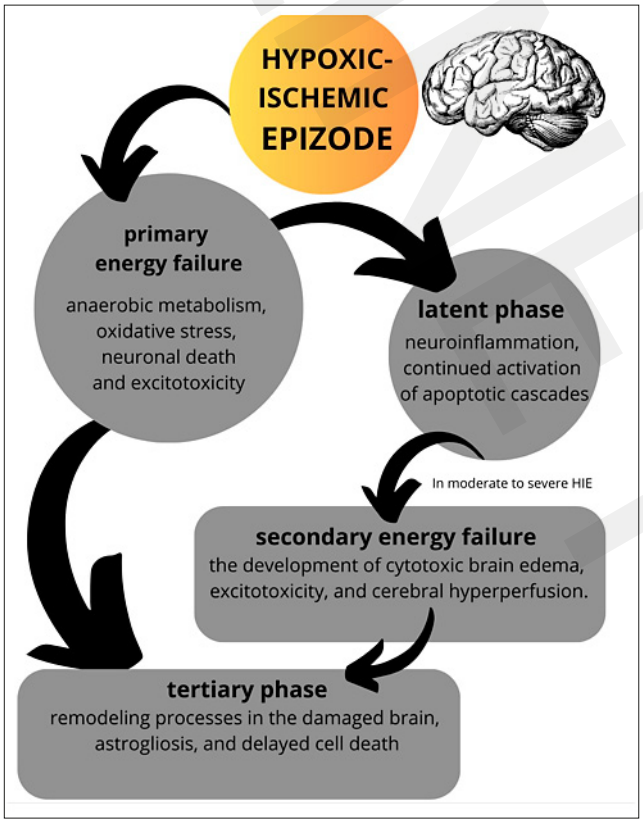

Figure 2. Criteria for inclusion in standard treatment [2,16]

Selective head cooling (SHC), whole body cooling (WBC), and combined hypothermia (CH). SHC uses a cap worn over the head inside which cold water circulates. This leads to uneven cooling – the strongest effect is on the cortical parts of the brain, followed by the central structures, and the weakest impact on the rest of the body. The head and brain reach a lower temperature than the rest of the body. The temperature in this procedure is 34–35 °C. A water circulating blanket is used for WBC: the cooling blanket is placed directly on the patient's skin or wrapped around the entire body, and is monitored and regulated by an external temperature control device, minimizing the risk of complications. In the WBC method, the target body temperature is between 33–34 °C. Both cooling devices monitor the temperature of the newborn with a probe and maintain the desired temperature by regulating the temperature of circulating water. TH should last 72 hours, after which a gradual temperature increase of 0.5 °C per hour is initiated [2]. Refrigeration lasting less than or longer than 72 hours and deeper cooling (above 5 °C) may weaken the neuroprotective effect [17]. Table 1 illustrates in detail the potential upsides and downsides of each method.

A narrow therapeutic window requires rapid action, often already during the transport of a neonate diagnosed with HIE to a more specialized centre. For this purpose, passive or active cooling is used [21, 22]. SHC and WBC are both types of active cooling. In passive cooling, unlike active cooling, no cooling devices are used, and the process itself involves turning off the warmer or incubator and exposing the baby's body by removing clothing and not covering the neonate with a blanket [2]. Studies on the effectiveness of passive cooling have yielded satisfactory results. Of 297 transported newborns, 263 had a temperature within the target range of 35 °C (±0.5 °C) [21]. A study comparing the short-term effects of passive and active cooling was also conducted. Sixty-three newborns were passively cooled, while 13 were actively cooled. No statistically significant difference was observed in the frequency of seizures or complications following TH treatment. In addition, actively cooled newborns had a higher chance of achieving the target body temperature upon arrival at a specialized centre. Moreover, imaging results obtained in this group of patients showed a greater degree of brain damage. However, these differences may not be sufficiently reliable due to the relatively large discrepancy in the group sizes [22].

A meta-analysis was also performed to assess the target body temperature range in newborns cooled using a servo-controlled cooling device (CTH) or without its use during transport. The analysis was based on eight studies, including a total of 517 children. It was shown that in the CTH group, body temperature, on average, was 0.82 °C lower, and there was less temperature variability. Therefore, it is likely that the use of CTH increases the chances of a newborn arriving at the centre within the target body temperature range. However, more research is needed on the short-term and long-term effects of this therapy to fully evaluate its effectiveness [23].

In a prospective cohort study involving 186 children, the effectiveness of three cooling methods was compared: passive (n=47), active using gel packs (n=36), and active using CTH (n=103). CTH has been found to reduce body temperature fluctuations during transport, and increase the likelihood of achieving the target body temperature upon arrival at a specialized centre. Furthermore, no statistically significant differences were found between the groups regarding mortality rates and the extent of MRI lesions.

On this basis, CTH was considered the most effective and preferred method [24].

Combined hypothermia treatment with pharmacotherapy. Despite the proven efficacy of TH, the treatment effectiveness remains unsatisfactory. In most clinical trials, high mortality rates, severe disability and neurological implications among newborns were still observed. Hence, current research on HIE aims to find a more effective solution [25]. It is believed that combining TH with pharmacotherapy yields the best outcomes in treating HIE [14].

A meta-analysis conducted at the University of Toronto, Canada, indicates that the use of neuroprotective agents reduces the hospitalization duration of newborns with HIE, compared to the group treated with TH alone. However, no impact of new therapies on reducing the risk of death or neurological disorders was proven. The compounds tested included phenobarbital, topiramate, magnesium sulfate, melatonin, erythropoietin (EPO), xenon, and stem cells. No superiority in effectiveness of any therapy over the others was demonstrated [26]. In the search for other neuroprotective therapies, a preclinical multi-drug screening study was conducted on rat models, using 25 promising agents.

The aim of the study was to select the best treatments, both in terms of future pharmacotherapy combined with TH and potential monotherapies. The effectiveness of the therapies was based on histopathological analysis of the percentage of brain areas lost. The average loss was 41.46% in the control groups, and was a pattern indicating an average brain injury. Eight agents effectively reduced brain damage. The best therapeutic effects were shown by caffeine, Sonic Hedgehog Agonist (SAG), allopurinol, melatonin, clemastine, and Omegaven. The results confirm the effectiveness and validity of using the aforementioned agents in neuroprotection and the treatment of HIE [27].

Erythropoietin (EPO) is a cytokine that functions as a growth factor for the red blood cell line usually used in children for anaemia due to chronic kidney failure. EPO mechanisms include increased neuronal and glial migration around the damaged area through the secretion of matrix metalloproteinases, as well as binding to the homodimeric cell surface receptor (Epo-R) expressed by brain cells, which prevents apoptosis [25, 28]. Despite its neuroprotective properties shown in rodent studies, such as reduced cerebral infarct, enhanced oligodendrocyte survival, sensorimotor function, cognitive response, anti-inflammatory and anti-oxidative effect in the brain [25] – clinical trials have not yielded such favourable results. A large meta-analysis comprising 903 infants did not show a statistically significant difference in improving risk of death. The study reported different dosing regimens and routes of administration (intravenous or subcutaneous) [28].

Another criterion that was not met was a reduction in the mortality rates and the incidence of neurological disorders. Moreover, a higher incidence of serious adverse events, mainly cardiovascular, i.e. hypertension, thrombosis, hypercoagulability, disseminated intravascular coagulation (DIC), intracranial haemorrhage, and others, were observed in a randomized, multicentre clinical trial conducted on 501 newborns born at ≥36 weeks of gestation with moderate or severe HIE, who received a dose of 1,000 U per kg of EPO or equivalent volume of saline in four intravenous injections [29]. However, there are also studies that show the positive effect of EPO on the body of the newborn.

The efficacy of EPO in combination with mild therapeutic hypothermia (MTH) was studied in terms of its impact on oxidative stress and neuroprotection in neonates. The study was conducted on a group of 90 newborns with HIE divided into two equal groups. EPO (1,000 IU/kg body weight via intramuscular injection) or placebo was administered in the same schedule [30]. In the EPO group, survival was twice as high as in the control group. In addition, a lower incidence of complications, fewer deaths and post-therapeutic interventions were observed in this group of newborns. It was also shown that EPO therapy in combination with MTH reduces oxidative stress in children with HIE and is more effective than other methods currently in use, such as Neuroprotective Effect of Sovateltide, Cell-Based Treatment and MTH alone [30]. Faced with these results, more research should be conducted to standardize the dose, route, and period of administration, as well as to assess whether combined EPO and HIE therapy would be appropriate in both preterm and in-term infants [28].

In recent years, there has been increased emphasis on exploring therapeutic options with umbilical cord stem cells (USC) using their neuroprotective and neuroregenerative properties potentially creating new ground in the various treatments in neonatal diseases, such as bronchopulmonary dysplasia, preterm brain injury, congenital heart disease and congenital diaphragmatic hernia [31]. Other advantages of stem cells were paracrine anti-inflammatory effects (through the release of anti-inflammatory cytokines), stimulation of brain angiogenesis by increased vascular endothelial growth factor (VEGF) synthesis, oxidative stress alleviation, prevention of caspase-3-mediated apoptosis, secretion of brain-derived neurotrophic factor with neuroprotective properties and anti-astrogliosis effects. There were also no ethical issues when it comes to USC acquisition – USCs are collected from non-embryonic and non-neural tissue, which is umbilical cord tissue [31, 32].

Research on the effects of stem cells on the brain so far includes both animals and some clinical studies [33,34]. Among the on-going trials we can distinguish the SHIELD study being a phase I, open-label, non-randomised trial evaluating this feature during CL2020 cells implementation. After prior preparation, CLCL2020 cells are administered intravenously to neonates between 5–14 days after birth [33]. Despite some promising results, further study is still needed [34].

Another interesting approach is a microRNA (miRNA) supplementation using mesenchymal stem cell-derived extracellular vesicles. miRNAs, also known as small non-coding RNAs, influence the functioning of the entire organism by regulating gene expression through the messenger RNA degradation or translation inhibition. A strong advantage of its formulation is good blood-brain barrier permeability which allows efficient regulation of pathogenesis pathways. Also, miRNA are responsible for metabolic pathways regulation, protein expression and immune response management with its neuroregenerative, anti-apoptotic and anti-inflammatory properties, especially in the miR-21 miR-124, miR-126, miR-146a molecules and miR-17–92 cluster [35].

Allopurinol, a xanthine oxidase inhibitor, is considered a free radical scavenger which prevents the production of ROS. In a preclinical study on rat models, a combination of allopurinol and TH was used to determine its effect on oxidative stress. The rats were divided into five groups: 1) control, 2) experimental trial with hypoxia and ischemia (HI), 3) HI + TH, 4) HI +

allopurinol, and 5) HI + TH + allopurinol. In the last two groups, allopurinol was administered as a single intraperitoneal injection at a dose of 135 mg/kg, 15 minutes after the hypoxia procedure. In all groups subjected to any treatment, reduced levels of oxidative proteins in plasma and a decrease in lipid peroxidation in the hippocampus and cortical-subcortical area were observed. Additionally, the least changes in the brains of the animals were observed in the groups treated with TH and TH with allopurinol. Moreover, after the neuroprotective therapies, both short-term and long-term improvements in animal function were noted. It is possible that the future inclusion of allopurinol prior to the initiation of TH will allow faster drug concentration in the cerebrospinal fluid (CSF) and avoid excessive oxidative stress associated with HIE, which should be confirmed in subsequent studies [36]. Currently, an international, multi-centre Phase 3 clinical trial is being conducted to assess the effects and safety of using allopurinol in combination with TH for the treatment of HIE in near-term and term newborns. The primary inclusion criteria for the programme are developing HIE and severe perinatal acidosis. According to the assumptions, allopurinol or mannitol were administered by infusion through secure venous access in a single dose (20 mg/kg in 2 ml/kg of sterile water for injection) within 30 minutes after birth, with a second dose, half the size, given 12 hours later, but only to newborns previously treated with TH. At this moment, there is no information regarding the results obtained. In the future, the analysis of the efficacy of allopurinol will assist in determining more precisely whether it can be used as a neuroprotective agent in the treatment of HIE [37].

Caffeine (1,3,7-trimethylxanthine), is one of alkaloids with anantagonistic effect on adenosine receptors, inhibiting the GABAA receptors and phosphodiesterase which influences the nervous system through several reactions. Methylxanthines including caffeine have anti-cancer, immunomodulatory, anti-oxidative, anti-apoptotic and anti-inflammatory properties in the brain, and are therefore considered to be neuroprotective agents. These qualities explain why the therapeutic potential of caffeine is being tested in various diseases, such as Parkinson's, Alzheimer's, apnea of prematurity, cardiovascular disease, rheumatoid arthritis, multiple sclerosis, ocular diseases, bronchopulmonary dysplasia, patent ductus arteriosus, retinopathy of prematurity, depression, and hydrocephalus, among others [38–40].

A meta-analysis of preclinical studies based on seven animal studies using caffeine, found overall sensorimotor improvement, increased cortical volume (n=2), reduced brain tissue atrophy (n=2), apoptosis alleviation (n=2), and in individual studies reduced brain infarct volume, microglial activation and decreased the level of interleukin-6. In six of seven studies, caffeine was administered intraperitoneally, while in the remaining study it was administered through drinking water to lactating dams [39]. In other studies in rats with HI brain injury, caffeine was administered intraperitoneally (15, 20, 40, or 120 mg/kg) before HI, and again 24 and 48 hours after HI. One group received the first dose of 40 mg/kg after HI, and then two doses at 24 and 48 hours after HI. The 120 mg/kg dose increased mortality, while lower doses showed neuroprotective effects, with the strongest effect observed after administration of 40 mg/kg before HI [41]. A retrospective, multicentre study of 52 neonates with HIE treated with combined TH and methylxanthines, including 28 treated with caffeine for 1–18 days, showed a rather pessimistic picture. Compared with the control group, the caffeine group had higher mortality rates (10% and 14%, respectively), and longer hospitalization, although these data may be confounded by the fact that infants with severe HIE were more likely to get additional therapy in the form of methylxanthines. Another limitation of the study was the lack of documentation of brain imaging, as well as uncertainty regarding the dosage and timing [40].

Based on preclinical studies, melatonin is also considered a potential neuroprotective agent [27]. Three receptors – MT1, MT2, and MT3 – have been shown to be present in foetal brain tissue and leptomeninges, with which melatonin can interact to promote brain development. Moreover, melatonin upregulates the synthesis of anti-oxidant enzymes and exhibits anti-apoptotic effects in the brain [25]. To assess its effectiveness in combination with TH in the treatment of HIE, a meta-analysis summarizing therapeutic effects from five clinical studies (215 newborns; enteral, oral, or intravenous administration) was performed. The mortality rate analysis based on two clinical trials showed no differences between melatonin+TH treatment and TH treatment alone. Due to the insufficient amount of data, it was not possible to determine the impact of the new therapy on the subsequent neurobehavioral development. However, due to the low quality of the studies, the effectiveness of melatonin monotherapy in the treatment of HIE cannot be assessed [42].

2-arachidonoyl-sn-glycerol (2-AG) is one of the endogenous endocannabinoids which are responsible for activating the endocannabinoid system. This system is involved in processes related to brain development. Preclinical studies were also conducted on the efficacy of 2-AG together with TH in the treatment of HIE in rats. The effectiveness of the therapy was assessed based on medium- and long-term outcomes. Pathomorphological analysis of brain lesions seven days after the hypoxic-ischemic incident showed that in rats treated with 2-AG (administered as an intraperitoneal injection), the brain infarct areas were significantly smaller compared to untreated animals. Additionally, the treated animals had a significantly larger ipsilateral hippocampus area and higher cellularity. Similar results were obtained in the control group. At 90 days of age, the damage area in the brain was still smaller in treated animals, but the differences were not statistically significant. The 2-AG treatment yielded a long-term beneficial neuroprotective effect; thus, 2-AG therapy could potentially be an alternative to TH in treating HIE in developing countries [43].

Granulocyte-colony stimulating factor (G-CSF) is a glycoprotein and one of the haematopoietic growth factors. The G-CSF role is not only limited to the management of neutrophil count, but also is responsible for the neuroprotective effect that is used in many experimental models [11]. Preclinical studies in rodents have shown that G-CSF intraperitoneal injection induced upregulation of the G-CSF receptor, diminished brain infarct volume, oedema, inflammation (by shrinkage of inflammatory mediators, such as interleukin-1β and tumour necrosis factor-α), and mortality rate, anti-apoptotic effect, ameliorated neurogenesis and angiogenesis [11,44]. Hu et al. investigated the effect of colony stimulating factor 1 (CSF1) in a rat model with hypoxic-ischemic-induced brain injury by prior ligation of the right common carotid artery followed by 2.5 hours of hypoxia and intranasal administration of recombinant human CSF1. The result was a decrease in brain infarct

volume, local oedema, and had an anti-inflammatory effect in the brain tissue [12]. Despite significant advantages, clinical studies clarifying the effect of G-CSF on neonatal HIE are still lacking [45].

Metformin is the primary drug used in diabetes type 2 mellitus [46]. In addition to regulating blood glucose and lipid levels, metformin has been shown to have neuroprotective, anti-oxidative, anti-inflammatory and promote angiogenesis due to the activation of AMP-activated protein kinase (AMPK), and suppression of rapamycin pathway target (mTOR) [46,47]. Interestingly, in one neuronal cell culture study, metformin turned out to be insufficiently effective, although it is worth noting that the study only investigated the effect on phase I of hypoxia-ischemia [47]. On the other hand, in mice models some studies have shown that metformin treatment (via subcutaneous injection), both one day and seven days after a hypoxic-ischemic event, determines the optimistic prognosis [48,49].

There are more experimental and clinical studies describing various neuroprotective agents that potentially could be used as novel therapies in HIE treatment. Substances like exenatide [25], clemastine, N-acetylcysteine (NAC) [27], polyunsaturated fatty acids, deferoxamine, osteopontin, noble gases, leptin, magnesium sulphate and plant-delivered polyphenols [10], belong to this group. It is difficult to be precise about their effectiveness due to the limited number of data; therefore, more high-quality studies are needed to prove their promising effects and determine if they can be considered as potentially successful novel therapies combined with standard TH.

Validity of the use of therapeutic hypothermia in low-income countries. While TH remains one of the most significant treatment options for neonatal HIE, various studies indicate that the incidence of HIE is higher in the low-to-middle income countries than in high income countries [2,50]. This discrepancy in HIE prevalence poses the question whether TH also remains as much of an effective treatment option in developing countries as it is in developed countries.

A randomized controlled trial (HELIX trial, RTC) published in 2021, suggests that in low-to-middle income countries TH does not reduce the morbidity of neonates with HIE. RTC was conducted in tertiary hospitals in India, Bangladesh and Sri Lanka, and included 408 eligible infants randomly assigned to control and TH treatment groups. The 72 infants treated with TH died before they were discharged from hospital. The causes of death included asphyxial brain injury-related complications, persistent pulmonary hypertension, subgaleal or intracranial bleed, and complex congenital heart disease. In contrast to this, in the control group 49 infants died because of similar complications. After hospital discharge, 12 infants from the TH treatment group died and 14 from the control group, respectively.

Data gathered in the above trial indicates that unlike in developed countries, TH in developing countries does not reduce hypoxic ischaemic brain injury shown on MRI, and increases the incidence of infant death. Furthermore, when using TH as a treatment method in low-to-middle income countries, not only does the morbidity increase, but several adverse outcomes were also noted, such as hypotension, metabolic acidosis, thrombocytopenia, gastric bleeding and prolonged hospital stay [51]. Research suggests it is likely that the disparities in healthcare systems, such as inadequate equipment, inexperienced medical staff and low funding, might have significantly contributed to the gap between developed and developing countries [50].

SUMMARY

Neonatal HIE is often associated with serious consequences, such as neurodevelopmental impairment, cerebral palsy, epilepsy, and in some cases even lead to death despite the treatment. Although TH still has some strong advantages, it also has some limitations: numerous inclusion criteria, decreasing effectiveness with the severity of HIE, and side-effects of treatment, the high cost of the procedure, and the requirement of specialized staff to guarantee satisfactory results. Regarding the standard HIE therapy, the lack of funds and limited technical development in low-income countries and potential harm in the case of infection warrants further research to discover the most suitable treatment patterns.

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