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Review

Analgesics, sedatives, anticonvulsant drugs, and the cooled brain

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SUMMARY

Multiple randomized controlled trials have shown that prolonged, moderate cerebral hypothermia initiated within a few hours after severe hypoxia–ischemia and continued until resolution of the acute phase of delayed cell death reduces mortality and improves neurodevelopmental outcome in term infants. The challenge is now to find ways to further improve outcomes. In the present review, we critically examine the evidence that conventional analgesic, sedative, or anticonvulsant agents might improve outcomes, in relation to the known window of opportunity for effective protection with hypothermia. This review strongly indicates that there is insufficient evidence to recommend routine use of these agents during therapeutic hypothermia. Further systematic research into the effects of pain and stress on the injured brain, and their treatment during hypothermia, is essential to guide the rational development of clinical treatment protocols.

1. Introduction

Moderate to severe neonatal hypoxic–ischemic (HI) encephalopathy occurs in about one to three cases per 1000 term live births in the developed world, and is associated with long-term neurodevelopmental disability in survivors [1]. Excitingly, large randomized controlled trials have now confirmed that prolonged moderate cerebral hypothermia in term infants with moderate to severe encephalopathy, started within a few hours after birth and continued until resolution of the acute phase of delayed cell death, reduces structural brain injury and improves neurodevelopmental outcome in the medium to long term [2–4]. The major clinical challenge now is that current therapeutic hypothermia protocols are incompletely neuroprotective, reducing the combined risk of death and severe disability at 18 months of age by ~12% [2]. Thus, given that many children continue to die or survive with disabilities despite treatment with hypothermia, it is now critical to find ways to improve current treatment protocols. This review critically assesses whether stress or pain may prevent hypothermia from protecting the brain, and whether treatment with analgesics, sedatives or anticonvulsants may help augment hypothermic neuroprotection.

The potential significance of these factors can only be understood in relation to the evolution of HI injury. The central insight that underpinned development of therapeutic hypothermia was that there can be a significant latent phase after resuscitation in which the hypoxia-induced impairment of cerebral oxidative metabolism, cytotoxic edema, and accumulation of excitatory amino acids can at least partially recover, many hours before the development of irreversible failure of mitochondrial function (Fig. 1) [5]. Critically, electroencephalographic (EEG) activity remains suppressed during the latent phase despite normal or even increased levels of high-energy phosphates. After moderate to severe insults, this period is followed by progressive secondary deterioration from about six to 15 h, as shown by delayed onset seizures, brain cell swelling and accumulation of excitotoxins, near-complete and irreversible failure of cerebral mitochondrial activity, and ultimately spreading cell death [6].

The preponderance of evidence strongly suggests that it is in the latent phase that interventions can reduce or increase brain injury, and that later interventions have limited or no effect. Mild hypothermia started in the latent phase (typically within the first 6 h) after severe HI, and continued for up to 72 h, reduced secondary cell loss, and improved neurophysiological recovery in near-term fetal sheep [5]. By contrast, the same duration of mild head cooling started 8.5 h after cerebral ischemia, after the onset of secondary seizures in this paradigm, was not significantly protective [5]. Thus, treatments started within the first 6 h after HI are most likely to affect neural outcomes.

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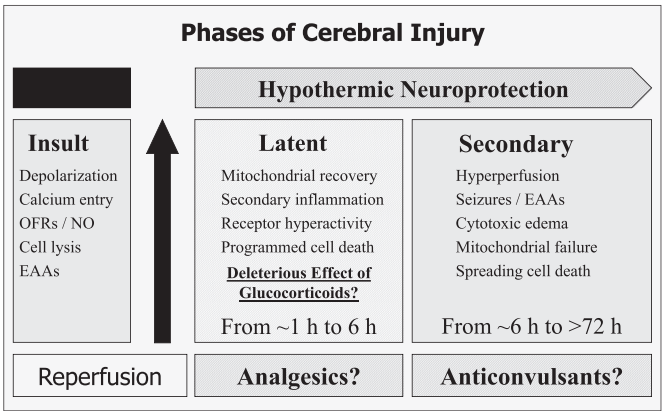

Fig. 1. Schematic diagram illustrating the different pathological phases of cerebral injury after severe hypoxic–ischemia. OFR: oxygen free radicals; NO: nitric oxide; EAA: excitatory amino acids.

2. Stress and newborn infants with HI encephalopathy

Infants with HI encephalopathy have by definition been exposed to a severe period of HI, typically leading to multi-organ dysfunction and injury. In addition to neural injury, this commonly includes myocardial damage leading to hypotension, impaired hepatic and renal function, respiratory dysfunction requiring respiratory support, and delayed onset, generalized seizures [5,7]. These complications often require painful or stressful medical procedures such as mechanical ventilation and venepuncture. Consistent with this, neonates needing mechanical ventilation have elevated serum beta-endorphin, cortisol, catecholamine, and glucose levels [8,9]. Similar increases in serum cortisol levels and sympathetic activity are seen after severe asphyxia without ventilation in the fetal sheep, and presumptively help support arterial blood pressure during cardiac dysfunction [10,11].

Induced hypothermia is a significant physiological stress in its own right [12]. For example, in the fetal sheep, mild hypothermia was associated with more prolonged elevation of circulating cortisol levels after asphyxia [13]. Similarly, in the piglet, plasma cortisol levels during recovery from HI were higher during hypothermia than normothermia [14]. There is evidence that exposure to exogenous glucocorticoids after asphyxia can increase neuronal loss in preterm fetal sheep [10], and thus increased endogenous cortisol could be deleterious. Nevertheless, therapeutic hypothermia itself has not been associated with any apparent overall increase in systemic complications of asphyxia in large randomized controlled trials [2].

3. Analgesics and the physiological responses to pain and stress

It is important to appreciate that although a stimulus triggers physiological responses, it may not necessarily be perceived as painful when consciousness is impaired by encephalopathy [15]. Nevertheless, infusion of analgesics such as morphine significantly reduce plasma cortisol and noradrenaline concentrations in ventilated newborns compared with placebo treatment [9,16]. However, it is still unknown whether analgesic infusions during hypothermia reduce these stress responses, and clinical practice is highly variable because of the lack of clear evidence. Some randomized trials of hypothermia for encephalopathy consistently used opiates, but most used analgesics or sedatives at the discretion of the attending clinicians [17]. It is unknown whether this difference affected the overall benefit associated with hypothermia in these trials [2].

Of concern, in ventilated preterm neonates pre-emptive morphine infusions decreased signs of pain but did not improve neural outcomes, whereas intermittent morphine treatment was associated with increased risk of death or brain lesions [18]. Moreover, hypothermia reduces the clearance of morphine, and higher-dose infusions based on clinical state can lead to potentially toxic levels of morphine in newborn infants [19]. Thus, it would be unwise to presume that pre-emptive analgesic use during therapeutic hypothermia is harmless.

4. Are sedation or pain relief during therapeutic hypothermia beneficial after asphyxia?

Thoresen et al. reported that mild hypothermia for 24 h was not protective after HI in unsedated piglets [14], whereas they have found consistent protection with the same degree of cooling in piglets receiving either halothane anesthesia for at least 5 h or intravenous anesthesia with propofol and remifentanil [20,21]. The significance of these findings is unclear. Not only were the protocols not directly compared, but 'sedation' was achieved with general anesthetic agents, not simple analgesics. There is increasing evidence that some general anesthetic agents can be protective in rodent models after cerebral ischemia, as recently reviewed [22]. By contrast, in adult pigs no significant improvement in neuronal damage was found with isoflurane ventilation for 1 h immediately after cardiac arrest [23], although this may have reflected an insufficient duration of treatment. Indeed, neuroprotection with prolonged mild to moderate hypothermia after HI has been consistently observed in unsedated/unanesthetized fetal sheep, and neonatal rodents [5].

Speculatively, these contrasting results could partly reflect differences in adaptation to hypothermia between species. Human newborn infants and fetal sheep rely on non-shivering thermogenesis by brown fat during hypothermia [12], and neonatal rodents rely on huddling, whereas the piglet does not have brown fat, and instead shivers during hypothermia [14]. Potentially, intense shivering in piglets might have been associated with greater systemic disturbances than in species that do not shiver, and analgesic/anesthetic treatment may have suppressed shivering, as seen in adults [24].

5. Are analgesic agents neuroprotective after hypoxia–ischemia?

There is little preclinical evidence that analgesic and sedative agents improve histological or behavioral outcomes after HI. Opiates have been reported to reduce oxidative damage in isolated brain mitochondria exposed to 5 min of anoxia followed by reoxygenation for 5 min [25]. However, after HI in postnatal day 7 (P7) neonatal rats, a continuous infusion of morphine in clinical doses did not affect neuronal damage after seven days recovery; indeed, high-dose therapy (1 mg/kg/h) was associated with significantly poorer weight gain [26]. Similarly, in P10 rats (broadly equivalent to the full-term human infant) morphine treatment was associated with reduced survival and no significant differences in the volume of infarction, weight gain, or behavioral outcomes [27]. No studies of combined treatment of therapeutic hypothermia with opiates were identified after a systematic PubMed search.

6. Other sedative agents: the α_2-adrenergic agonists

The latent phase is associated with suppressed EEG activity, and reduced brain blood flow and metabolism [6]. There is increasing evidence that this suppression is actively mediated by endogenous inhibitory neuromodulators, including noradrenaline acting