J. of Obst. & Gyn. of India Vol. 52, No. 2 : March/April 2002 Pg 30-34

Review Article

Cerebral Hypothermia as a Neuronal Rescue Strategy

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Summary

Brain temperature is considered a critical determinant of the severity of brain injury. Clinical as well as experimental evidence strongly suggests that hypothermia has a powerful neuroprotective effect against hypoxic-ischemic brain injury, whereas hyperthermia works contrarily. Accumulating evidence now indicates that the brain injury of the fetus may be more exacerbated under maternal hyperthermia.

Hypothermia has been currently applied clinically to adult patients following cerebral injury and is also being tested for its usefulness on newborn infants with hypoxic-ischemic encephalopathy. Although its clinical use to newborn is limited at the present time, it appears to possess a great potential to become a new modality for perinatal hypoxic-ischemic encephalopathy.

Introduction

Fetal heart rate (FHR) monitoring was introduced in the 1960s for intrapartum fetal surveillance. Its effectiveness in reducing the perinatal mortality has been confirmed by a number of randomized trials (American College). The prevalence of neurological impairment, however, such as cerebral palsy or mental retardation, has not been altered significantly since it became widely accepted for clinical use (Nelson et al 1996). Indeed the relative lack of efficacy is partially due to the fact that there are so many different causes responsible for cerebral palsy that the intrapartum events are less, an incidence of approximately only 10% of all cerebral palsy (Nelson and Ellenberg, 1986; Blair and Stanley 1988; Nelson 1988), than had been generally considered. It may be due to the variation or unreliability of interpretations of the FHR patterns and the inability to perform optional management in the face of asphyxiation pattern, according to several studies (Pancth et al 1993, Kirth et al 1995; Richmond et al 1994; Goffney et al 1995; Parer 1997). They estimate that the incidence of cerebral palsy would be reduced by several percents (Richmond et al 1994; Goffney el al 1995) if the FHR tracing could have been interpreted properly and optimal obstetric care performed. Therefore the National Institutes of Health Committee recently proposed to standardize the terminology to interpret fetal heart rate patterns (National Institute of Child Health 1997) in the hope to reduce the incidence of cerebral palsy (Parer and King 2000).

Once intrapartum brain damage unfortunately occurs, the current clinical managements shift from prevention to rescue of neuronal damage after birth. There have been no medications or strategies yet proven to be useful to ameliorate the neuronal damages in clinical situation (Vannucci and Perlman 1997). Therapeutic interventions have been, thus far, restricted to be supportive and only aiming to reduce cerebral edema arising from hypoxia-ischemia.

Recently, however, cerebral hypothermia therapy has just started its application on the newborn infants with hypoxic-ischemic encephalopathy. (Thoresenand Whitelaw; 2000; Battin et al 2001, Azzopardi et al 2000). This technique has already been applied to adult patients following cerebral insults with some favorable results in reducing neurological sequelae (Marion et al 1997; Schwab et al 1998). Although its clinical use to newborn is limited at the present time, it appears to possess a great potential to become a new modality for perinatal hypoxic-ischemic encephalopathy. In this presentation, we discuss the current and forthcoming viewpoints of cerebral hypothermia as one of the future modalities of neural rescue strategy for the newborns experiencing hypoxic insults during perinatal period.

Historical use of cerebral hypothermia in neonates

Immersion in cold water used to be one of the resuscitative managements in 1950s and 60s for those infants born without spontaneous breathing. Westin et al 1959, Dunn and Miller (1969) and Westin (1971) studied its clinical usefulness and reported better neurological outcome of the infants who received the cold water management than those with the standard care of resuscitation at that time. Since Silvermann et al (1958) reported the importance of adequate thermal environment for a newborn in 1958, especially for preterm infants, hypothermia for a newborn became considered extremely hazardous, and thus, any clinical application of hypothermia to a neonate was abandoned until recently. With the concept of "not too cold to the infant", the technology to maintain an infant within the thermoneutral range was developed and the neonatal mortality, indeed, has been dramatically reduced. The problem of neonatal hypoxic-ischemic encephalopathy has persisted although a variety of neuronal rescue strategies has been intensively investigated.

Effects of cerebral temperature modulation

Hypothermia during or after hypoxic insults on the brain is now known to be neuroprotective, whereas hyperthermia has been proved to have the opposite effect on brain injury. It is now considered that brain temperature is a critical determinant of the severity of brain injury, and that its modulation can either ameliorate or exacerbate the neurological outcomes.

Cerebral hypothermia

Cerebral hypothermia can be divided into two main categories according to the timing of its application, intra-ischemic hypothermia and post-ischemic hypothermia. Intra-ischemic hypothermia, the neuroprotective effect of which was first reported in 1987 by Busto et al is now considered most promising. Lowering brain temperature by only a few degrees during hypoxia-ischemia leads to a long-lasting histological and functional neuroprotection, which subsequently has been repeatedly demonstrated by many studies using various animal hypoxic-ischemic models. (Green et al 1992; Nurse and Carbett 1994; Yager et al 1993). There are, however, few clinical situations to which hypothermia can be realistically applied during insult. Its clinical application, therefore, is restricted to the prevention of anticipated brain injury, such as hypothermia during heart surgery.

On the other hand, the application appears more practical after an event. The neuroprotective effect of post-ischemic hypothermia was first reported by Busto et al. 1992. The effect was, at first, considered to be transient and merely to postpone the neuronal damage process even if hypothermia was initiated immediately after the insult (Dietrich et al 1993). This was due to a relatively brief duration (0.5-3 hours) in the early experiments, and it is now understood that long-lasting neuroprotective effects can be accomplished if hypothermia is prolonged to 12 hours or more. Colbourne and Orbett (1994) first demonstrated that prolonged hypothermia for 24 hours after the insult revealed long-lasting neuroprotective effects in adult gerbil. Recent studies (Corbett et al 2000; Bona et al, 1998) also demonstrated its effectiveness even if the initiation of hypothermia was delayed several hours after the insult (Colbourne et al 2000; Gunn and Gunn 1998; Gunn et al 1998) Hypothermia after the insult is more feasible and can be applied to a variety of clinical situations.

Cerebral hyperthermia

The effects of hyperthermia on brain injury has also been investigated. Contrary to hypothermia, hyperthermia during or after the insult exacerbates the brain injury (Yager et al 1993; Dietrich et al 1990; Ninamisawa et al 1990; Laptook 1994). Minamisawa et al (1990) reported that it could increase the brain damage by 20% per degree in the adult rats. Hyperthermia after the insult is also believed to be harmful for brain injury, although there have been fewer studies. Kim et al (1996) reported 3 hour hyperthermia initiated 24 hours after the insult significantly exacerbated brain injury in adult rats.

Mechanisms of perinatal brain injury

The mechanisms of hypoxia-ischema induced brain injury are complex and involve several different or

overlapping cascades, such as neurotransmitter release, influx of calcium, NO and free radical formation and blood-brain barrier alterations (Dietrich et al 1990). These cascades result in neuronal cell death via necrosis or apoptosis. Necrosis is a rapidly occurring form of cell death by the alterations in ionic homeostasis, whereas apoptosis is a delayed form of cell death by the activation of genetic program (Banasial et al 2000). In addition, the extent to which these cascades are associated with brain injury is much influenced by age (Yager and Thornnill, 1997; Vexler and Ferriero, 2001).

The immature brain retains a part of the apoptotic cell death program which is essential for antenatal development and this can be easily activated by hypoxia-ischemia. (Waite et al). Indeed, recent evidence shows that one of the characteristic differences between mature and immature brain injury is the type of cell death. Sidhu et al (1997) investigated age dependence of hypoxia-ischemia induced neuronal cell death using light microscopy and reported that apoptosis was the most prevalent type of cell death in the developing nerve system. Hu et al (2000) showed that the involvement of caspase-3 in the pathogenesis of cell death after hypoxia-ischemia declined along with neuronal maturation. Caspase – 3 is a cysteine protease which is essential and specific for apoptosis (Srini Vasan et al 1998; Arnstrong et al, 1997; Namura 1998) and when it is activated, it cleaves endogenous substrate proteins such as caspase-activated DNAase (ICAD), and finally causes apoptosis (Enari et al 1998).

Role of hypothermia

It is still unclear which cascade is an interventional point of hypothermia against hypoxic-ischemic brain injury. Several studies with adult animal models have shown that hypothermia reduced neurotransmitter release (Busto et al 1989) and hydroxyl radical production (Kil et al, 1996) suppresses nitric oxide synthesis (Karder et al, 1994) and prevents the development of cerebral edema (Lo Steinberg 1992) and blood-brain barrier alterations (Dietrich et al 1990). More recent evidence also substantiates that hypothermia inhibits apoptosis. Edwards et al (1995) first reported that hypothermia for 12 hours following hypoxia-ischemia reduced the fraction of apoptotic cells but had no effect on the fraction of necrotic cells in newborn piglets. They suggested that hypothermia may have specifically inhibited the apoptosis in the developing brain. Niwa et al (1998) demonstrated that the inhibition of DNA fragmentation was proportional to the magnitude of hypothermia in the hippocampal CAI region in adult gerbils. An increased anti-apoptotic protein Bcl-2 and a decreased pro-apoptotic protein Bax (Thang et al 2001; Inamasu et al 2000) induced by hypothermia were also observed.

We have demonstrated that post-ischemic hypothermia revealed an excellent inhibitory effect against caspase-3 activation (Fukuda et al, 2001; Tomimatsu et al, 2001) and that the inhibition of caspase-3 activation may be an interventional point underlying the neuroprotective effect of hypothermia in neonates. As previously mentioned, caspase-3 is considered to play a major role in cell death in the immature brain but minor role in mature brain after hypoxic-ischemic brain injury. We believe that the neuroprotective function of hypothermia is more effective in the immature brain, and that the use of hypothermia possesses a great potential if it becomes clinically applicable to neonatal hypoxic-ischemic encephalopathy.

Intrapartum Hyperthermia

Although intrapartum events per se are hypoxic-ischemic processes, the fetus can compensate for hypoxia-ischemia with a complexly regulated redistribution of blood flow to the brain, myocardium and adrenal glands at the expense of most other organs. But when the physiologic compensations become overwhelmed as the severity of hypoxia increases, acidosis becomes prominent and the cardiac output and thus cerebral perfusion fall. Intrapartum fetal heart rate monitoring can help physicians identify such conditions as feal hypoxia and acidosis (Murata et al 1982). When the FHR patterns are persistently nonreassuring and fetal acidosis is suspected, prompt delivery is recommended (American College, 1995).

With the presence of maternal hyperthermic condition, however, the clinical situation may significantly be altered. Fetal temperature normally exceeds maternal one by about 0.5 degree C. (Schroder and Power 1997). The diffierence becomes greater if the maternal temperature becomes higher. The brain injury may be more exacerbated under maternal hyperthermia when physiologic compensations are overwhelmed. Temperature rise by only a few degrees during hypoxia-ischemia can worsen the severity of the brain injury. Several recent clinical studies (Liebermann et al, 2000, Impey et al, 2001) suggest that maternal fever itself can be an independent risk factor for adverse neonatal outcome and it may become increasingly important to observe maternal temperature as well as FHR patterns for the prevention of fetal brain injury resulting from intrapartum hypoxia-ischemia.

Conclusion

Brain temperature is a critical determinant of the severity of brain injury. Hypothermia ameliorates the brain injury and hyperthermia exacerbates it. Hypothermia has already been utilized to adult patients following cerebral insults with apparent clinical success. For the newborn infants with hypoxic-ischemic encephalopathy its application has just started. Even before an application of hypothermia during intrapartum period at the present time, it is important to, at least, avoid intrapartum maternal fever for better neurological outcome of the neonates.

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