

Study of Head Cooling for Newborns with Hypoxic Ischemic Encephalopathy

Thesis

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Abstract

Despite major advances in obstetric and neonatal care, hypoxic-ischemic cerebral injury during the perinatal period is still a significant cause of death and severe long-term neurological impairment like cerebral palsy, mental retardation and epilepsy in children **(Ilves et al., 2009)**.

Neonatal encephalopathy (NE) in term or late preterm infant is 'a clinically defined syndrome of disturbed neurological function in the earliest days of life manifested by difficulty with initiating and maintaining respiration, depression of tone and reflexes, subnormal level of consciousness and often by seizure **(Pfister and Soll., 2010)**.

Until recently, there were no specific strategies for prevention of brain injury in term and near-term infants. Neuroprotection with brain-specific therapies has been well studied in the preclinical arena over the past 15 years, with the aim to block or dampen cascade of events triggered by hypoxia and ischemia. **(Shankaran., 2009)**.

Recent randomized controlled trials (RCTs) have shown that mild therapeutic hypothermia (TH) initiated within 6 hrs of birth reduces death as well as neurodevelopmental disabilities at 18 months of age in surviving infants **(Selway., 2010)**.

Hypothermia has been shown to be reduce cerebral metabolism, prevent edema and loss of membrane potential, decrease brain energy use, prolong the latent phase, reduce infarct size, decrease neuronal cell loss, and the extent of brain injury and epileptic activity, relieves the permeability of BBB and intracranial pressure, **(Shankaran., 2012)**.

Key words : Hypoxic ischemic encephalopathy , Head cooling.

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List of Abbreviations

AAP	American Academy of Pediatrics
ACOG	American college of obstetrics and gynecology
AEDs	Antiepileptic drugs
aEEG	Amplitude-integrated electro encephalography
APTT	Activated partial thromboplastin time
ATP	Adenosine triphosphate
AMPA	α -amino-3-hydroxyl-5-methyl-4-isoxazole-propionate
aSAH	Aneurysmal subarachnoid hemorrhage
BBB	Blood brain barrier
BP	Blood pressure
CBF	Cerebral blood flow
CNS	Central nervous system
Cranial US	Cranial ultrasound
CS	cesarean section
CSF	Cerebro spinal fluid
CT	Computed tomography
DIC	Disseminated intravascular coagulopathy
DWI	diffusion-weighted imaging
ECHO	Echocardiography
EEG	Electroencephalogram
FHR	Fetal heart rate
GI	Gastro intestinal
HIE	Perinatal hypoxic-ischemic encephalopathy
HR	Heart Rate
HT	Hypothermia
ICP	Intra cerebral pressure
ICU	Intensive care unit
INR	International normalized ratio
LFT	Liver function tests
MOD	Multi organ dysfunction
MRI	magnetic resonance imaging
NE	Neonatal encephalopathy
NMDA	N-methyl-D-aspartate
NOS	nitric oxide synthase
NSE	Neuron specific enolase

Abbreviations

PA	Perinatal asphyxia
RBCs	Red blood cells
REM	Rapid eye movement
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
TBI	Traumatic brain injury

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Introduction

Perinatal asphyxia (from the Greek term **sphyzein** meaning “stopping of the pulse”) is a condition caused by a lack of oxygen in respired air, resulting in impending or actual cessation of apparent life. Perinatal asphyxia, if persists, leads to progressive hypoxemia and hypercapnia with metabolic acidosis (**Sills, 2004**).

Perinatal hypoxic-ischemic encephalopathy (HIE) is an important cause of brain injury. It can result long-term neurologic complications varying from mild behavioral deficits to severe seizures, mental retardation, and/or cerebral palsy in the newborn (**Lai and Yang, 2011**).

The early identification of asphyxiated infants at high risk of adverse outcomes and the early selection of those who might benefit from neuro-protective therapies are required (**Ong et al., 2009**).

Until recently, there were no specific strategies for prevention of brain injury in term and near-term infants. Neuroprotection with brain-specific therapies especially brain hypothermia is a promising therapy for neuroprotection for encephalopathy presumably due to hypoxic ischemia (**Shankaran, 2009**).

Recent randomized controlled trials (RCTs) have shown that mild therapeutic hypothermia (TH) initiated within 6 hrs of birth reduces death as well as neurodevelopmental disabilities at 18 months of age in surviving infants (**Selway, 2010**).

Hypothermia has been shown to be reduce cerebral metabolism, prevent edema and loss of membrane potential, decrease brain energy use, prolong the latent phase, reduce infarct size, decrease neuronal cell loss, and the extent of brain injury and epileptic activity, relieves the permeability of BBB and intracranial pressure, helps to retains sensory motor function, and preserves hippocampal structures **(Shankaran, 2012).**

Aim of Work

This study was conducted to review the literatures as regards the perinatal anoxia, its relation to hypoxic-ischemic encephalopathy and the role of selective head cooling as a neuroprotective therapy in term and near term neonates with perinatal asphyxia and evaluate the benefits versus side effects of cooling on survival neonates.

Chapter 1

Hypoxic-Ischemic Encephalopathy

Definition

Hypoxic-ischemic encephalopathy (HIE) in a full-term infant is a clinically defined syndrome of disturbed neurologic function in the earliest days after birth manifested by difficulty in initiating and maintaining respiration, the depression of the muscle tone and reflexes, the subnormal level of consciousness and often seizures. HIE the resultant condition of a deficit in the oxygen supply to the brain (**Ilves., 2012**).

Despite major advances in monitoring technology and knowledge of fetal and neonatal pathologies, perinatal asphyxia or, more appropriately, HIE, remains a serious condition that causes significant mortality and long-term morbidity. Hypoxic-ischemic encephalopathy is characterized by clinical and laboratory evidence of acute or subacute brain injury due to asphyxia (i.e. hypoxia, acidosis). Most often, the exact timing and underlying cause remain unknown. (**Zanelli et al., 2015**).

Incidence

Internationally:

In the United States and in most technologically advanced countries, the incidence of hypoxic-ischemic encephalopathy is 1-4 cases per 1000 births .The incidence of hypoxic-ischemic encephalopathy is reportedly high in countries with limited

resources; however, precise figures are not available. Birth asphyxia is the cause of 23% of all neonatal deaths worldwide. It is one of the top 20 leading causes of burden of disease in all age groups (in terms of disability life adjusted years) by the World Health Organization and is the fifth largest cause of death of children younger than 5 years (8%) (**Zanelli et al., 2015**).

Although data are limited, birth asphyxia is estimated to account for 920,000 neonatal deaths every year and is associated with another 1.1 million intrapartum stillbirths. More than a million children who survive birth asphyxia develop problems such as cerebral palsy, mental retardation, learning difficulties, and other disabilities (**Zanelli et al., 2015**).

In Egypt, hypoxic-ischemic encephalopathy is not an un-common health problem in Egypt. It tops the list for morbidity because of its significant health and social burden (**El Metwally., 2006**). A study from Children's Hospital, Cairo University showed that hypoxic ischemic encephalopathy cases represented 12.2% of the admissions to the NICU and were responsible for 18.8% of deaths (**Seoud et al., 2005**).

Predisposing factors

Antepartum risk factors:

Intrauterine hypoxia occurs when the fetus is deprived of an adequate supply of oxygen. It may be due to a variety of reasons such as prolapse or occlusion of the umbilical cord, placental infarction and maternal smoking. Intrauterine growth restriction (IUGR) may cause or be the result of hypoxia. Intrauterine hypoxia can cause cellular damage that occurs within the central nervous system (the brain and spinal cord). This results in an increased mortality rate, including an increased risk of sudden infant death syndrome (SIDS) (**Rosenberg A., 2008**).

Moreover, antenatal risk factors also include maternal obesity, thyroid dysfunction, previous cesarean delivery, abnormal amniotic fluid volume mostly oligohydramnios, and abnormal fetal heart rate (FHR) tracing before labor such as recurrent late decelerations, recurrent variable decelerations, or bradycardia (**Locatelli et al., 2010**).

Intrapartum risk factors:

There are many causes of intrapartum asphyxia, the most common of which include the following: prenatal hypoxia (a condition resulting from a reduction of the oxygen supply to tissue below physiological levels despite adequate perfusion of the tissue by blood), umbilical cord compression during childbirth, occurrence of a preterm or difficult delivery, and maternal anesthesia (both the intravenous drugs and the anesthetic gases cross the placenta and may sedate the fetus) (**Steven M., 2010**).

Intrauterine asphyxia occurs when placental blood flow and gas exchange is interrupted as shown in **Figure(1)**. Such interruption may be caused by the factors shown in **Table (1)**.