INTRODUCTION

Hypoxic Ischemic Encephalopathy (HIE) is an incident that occurs to a fullterm infant when there is an insult of asphyxia, which is a lack of oxygen brought on by circulatory problems, such as clotting of placental arteries, placental abruption, or inflammatory processes prior to the birthing process. Therefore, HIE is a condition during the initial delivery stages of a neonate‘s life when a portion of the brain (cerebral hypoxia) or the entire brain (cerebral anoxia) is deprived of adequate oxygen supply and blood flow ***(Fatemi et al., 2009)***.

When oxygen deprivation (hypoxic) and minimal blood flow (ischemic) occurs, there is a potential result of brain injury (encephalopathy). This phenomenon can occur in a neonate due to asphyxia during birth ***(Grow and barks, 2003).***

Perinatal asphyxia, more appropriately known as hypoxic-ischemic encephalopathy (HIE), is characterized by clinical and laboratory evidence of acute or subacute brain injury due to asphyxia. The primary causes of this condition are systemic hypoxemia and/or reduced cerebral blood flow (CBF). Birth asphyxia causes 23% of all neonatal deaths worldwide ***(Grow and barks, 2003).***

Neonatal encephalopathy has emerged as the preferred term to describe central nervous system dysfunction in the newborn period ***(Dammann, 2011).*** The American College of Obstetricians and Gynecologists (ACOG) describes neonatal encephalopathy as a clinically defined syndrome of disturbed neurologic function in the earliest days of life in an infant born at or beyond 35 weeks of gestation, manifested by a subnormal level of consciousness or seizures, and often accompanied by difficulty with initiating and maintaining respiration and depression of tone and reflexes ***(ACOG, 2014).***

The terminology does not imply a specific underlying pathophysiology, which is appropriate since the nature of brain injury causing neurologic impairment in a newborn is poorly understood. While neonatal encephalopathy was once automatically ascribed to hypoxia-ischemia**,** it is now known that hypoxia-ischemia is only one of many possible contributors to neonatal encephalopathy. Whether a particular newborn's encephalopathy can be attributed to hypoxic-ischemic brain injury is often unclear ***(Sartwelle, 2009)***.

Some investigators require stringent criteria for using the term neonatal encephalopathy, such as two or more symptoms of encephalopathy lasting over 24 hours ***(Badawi et al., 1998),*** while others require no more than a low five minute Apgar score. However, the use of Apgar scores alone is problematic, as Apgar scores may be low due to maternal analgesia or prematurity, or can be normal in the presence of acute hypoxia-ischemic injury ***(Bartha et al., 2004).***

Following initial resuscitation and stabilization, treatment of HIE includes hypothermia therapy for mild to moderate encephalopathy as well as supportive measures focusing on adequate ventilation and perfusion, careful fluid management, avoidance of hypoglycemia and hyperglycemia and treatment of seizures ***(Stola and Perlman, 2008)***. Intervention strategies aim to avoid any further brain injury in these infants ***(Perlman, 2006).***

Neonatal (HIE) is an important cause of death and neurodevelopmental delay worldwide. Treatment for infants with hypoxic-ischemic encephalopathy was limited to supportive care for a long time, but efforts have been made to develop effective therapies. However, through several experimental therapies for hypoxic ischemic encephalopathy seemed promising none proved consistently successful in clinical studies ***(Kaandorp et al., 2010).***

Over the past two decades, experimental and clinical evidence has accumulated that a 3-4^{o}C reduction of body temperature maintained for at least 72 hours in newborns with hypoxic ischemic encephalopathy may reduce cerebral injury and improve neurological outcomes. Recent clinical trials have demonstrated that prolonged cooling of either the head or the whole body of neonates with HIE is safe and associated with reduced short-term mortality and morbidity at 18 months of age ***(Edwars et al., 2010).***

Hypothermia Treatment (cooling therapy) is defined by the National Institute of Child Health and Human Development (NICHD) as a safe and effective cooling treatment as a form of neuroprotective therapy for neonatal HIE. Therapeutic hypothermia is the medical treatment that lowers a patient's body temperature to help reduce the risk of ischemic injury to tissue following a period of insufficient blood flow ***(Wu and Grotta, 2013).***

Cerebral hypoxia-ischaemia results in reduced cerebral oxidative metabolism, cerebral lactic acidosis and cell membrane ionic transport failure; if prolonged there is necrotic cell death. Although rapid recovery of cerebral energy metabolism occurs following successful resuscitation this is followed some hours later by a secondary fall in cerebral high energy phosphates accompanied by a rise in intracellular pH, and the characteristic cerebral biochemical disturbance at this stage is a lactic alkalosis. In neonates, the severity of this secondary impairment in cerebral metabolism are associated with abnormal subsequent neurodevelopmental outcome and reduced head growth ***(Roth et al., 2008)***

Several adverse biological events contribute to this secondary deterioration, including: release of excitatory amino acids which activate N-methyl-D-aspartate (NMDA) and amino-3- hydroxy-5- methyl-4- isoxazolepropionate (AMPA) receptors on neurons and oligodendroglial precursors, accumulation of excitatory neurotransmitters, generation of reactive oxygen radicals, intracellular calcium accumulation and mitochondrial dysfunction. Whilst necrotic cell death is prominent in the immediate and acute phases of severe cerebral insults, the predominant mode of death during the delayed phase of injury appears to be apoptosis. Neuroprotective mechanisms need to interact with these mechanisms to have beneficial effect ***(Northington, 2001).***

Newborn hypoxic-ischaemic brain injury differs from injury in the adult brain in several ways: NMDA receptor toxicity is much higher in the immature brain ***(McDonald and Johnstone, 1991***). Apoptotic mechanisms including activation of caspases, translocation of apoptosis-inducing factor and cytochrome-c release are much greater in the immature than the adult ***(Wang et al., 2009).*** The inflammatory activation is different with less contribution from polymorphonuclear cells and a more prominent role of IL-18 whereas IL-1, which is critical in the adult brain, is less important. The anti-oxidant system is underdeveloped with reduced capacity to inactivate hydrogen peroxide ***(Hedtjarn, 2005).***

Neuronal damage and death after asphyxia occurs in different phases and pathways. Initially primary energy failure and oxidative stress are responsible for tissue injury followed by secondary activated long term processes like excitotoxicity, inflammation, and apoptosis. Hypothermia, which decreases the cerebral metabolism and possibly affects on many other ways is the first therapeutic intervention proven being able to improve neurological outcome ***(Laptook et al., 1995).***

The pathogenesis of perinatal hypoxic-ischemic brain damage is highly complex, and involves impaired blood-brain barrier permeability, energy failure, loss of cell ion homeostasis, acidosis, increased intracellular calcium, excitotoxicity, free radical mediated toxicity, growth factor deficiency or up-regulation and activation inflammatory cascade in immature brain ***(Ferrierro, 2005).***

Free radicals are highly reactive molecules generated predominantly during cellular respiration and normal metabolism. Imbalance between cellular production of free radicals and the ability of cells to defend against them is referred to as oxidative stress. Glutathione peroxidase (GPX) is a principal antioxidant enzyme and protects the cells against intracellular radicals and peroxides coming from the respiratory chain or other metabolic pathways. A number of studies documented that HIE were associated with increased production of free radicals in animal models ***(Rodrigo et al., 2005).***

In newborns, therapeutic hypothermia was first described as a method of reanimation by immersion in cold water. Later, experimental studies in adult models of hypoxic ischemic injury suggested that brief periods of post insult hypothermia offered neuroprotection. Moderate systemic or selective cooling of the brain has been shown to reduce brain injury in experimental human adult studies after events like stroke, trauma or cardiac arrest ***(Miller et al., 1976).***

Hypothermia that is proven to decrease brain damage following asphyxia has an additional beneficial effect on the hypoxic damage of other organs than brain. It is well known that in addition to brain injury neonatal asphyxia has a profound effect on the function of major organ systems. Pulmonary, cardiovascular, hepatic, renal and gastrointestinal dysfunction may evolve due to hypoxicischemic damage as a result of the temporary lack of oxygen supply ***(Sarkar et al., 2009).***

Mild hypothermia is safe with no serious side effects reported. Mild bradycardia, mild hypotension, arrythmias, mild thrombocytopenia and sclerema/edema have been described ***(Blackmon and stark, 2006).***

Mild hypothermia helps prevent disruptions to cerebral metabolism both during and following cerebral insults. Hypothermia decreases the cerebral metabolic rate for glucose and oxygen and reduces the loss of high energy phosphates during hypoxia-ischaemia ***(Erecinska et al., 2003)*** and during secondary cerebral energy failure, and reduces delayed cerebral lactic alkalosis. The simultaneous increase in cytotoxic oedema and loss of cerebral cortical activity that accompanies secondary energy failure is also prevented ***(Gunn, 1998).***

Many of the effects induced by mild hypothermia may help to reduce the number of cells undergoing apoptosis. Experimental and clinical studies indicate that the number of apoptotic neurons is reduced caspase activity is lessened and cytochromec translocation is diminished by mild hypothermia, and there may be an increase in expression of the anti-apoptotic protein BCl-2 ***(Zhang et al., 2001).***

Hypothermia is associated with increased mortality in the premature infant. Data in premature and fetal asphyxiated animals are controversial, with some studies showing no effect and others showing improvement ***(Bennet et al., 2007).*** There is currently no evidence that therapeutic hypothermia offers any benefit to infants <36 weeks' gestational age; the safety and efficacy of cooling in this population are unknown. Clinical trials in late preterm infants are in progress ***(Gunn and Bennet, 2008)***.

Aim of the Work

To clarify and provide direction to clinicians regarding therapeutic hypothermia for neonates of 36 weeks of gestation or greater with HIE using the most updated evidence-based information.

In this work we will explain the pathophysiology of HIE, management including cooling therapy and the evidence behind hypothermia treatment.

Also we will show types of cooling therapy, methods, re-warming technique, other supportive treatment needed, the effectiveness of cooling and its role in reducing mortality, cerebral palsy and neurological deficits in survivors.

Finally we will mention the effects on other systems of the body and side effects to ensure its safety.

ANATOMY OF BRAIN AND CEREBRAL CIRCULATION

To understand how the newborn brain can become damaged by lack of oxygen during childbirth, one must investigate both the clinical condition in the fetus and newborn, as well as underlying mechanisms that lead to neuronal destruction- The following is a review of relevant neuroanatomy and physiology, the precipitating hypoxic insult to the immature brain known as perinatal asphyxia, the associated neonatal neurological condition of hypoxic-ischemic encephalopathy and pediatric onset of cerebral palsy, and the current edologic theory of hypoxic brain damage, known as excitotoxicity. Once the problem is delineated, then an overview of neuroprotective strategies will be presented ***(Noble, 1996)***.

I. **Central Nervous System Anatomy:**

The central nervous system (CNS) is comprised of brain and spinal cord. The human brain, weighing about one pound at birth and three pounds as an adult, is divided into two basic parts, the forebrain or cerebrum, and the hindbrain, or cerebellum and brain stem. This study looks specifically at the cerebrum (cerebral cortex and basal ganglia) and upper brain stem (thalamus, hypothalamus and pineal gland), which will be the focus of the following anatomical review. Cerebral Cortex

The cerebrum, about 80% of the brain by weight, is divided into two cerebral hemispheres (right & left), each composed of four separate lobes, the frontal, parietal, temporal and occipital lobes and one combined area, known as the limbic lobe. The hemispheres communicate to each other through the corpus callosum, a central band of 300 million fibers which cross over the midline ***(Noble, 1996)***.

A. The cerebral cortex is the outermost area of neuronal tissue, the most complex and last developed. It is usually 1- 4 mm thick in adult humans, but its size depends on environmental “enrichment" during the early neonatal developmental period, primarily because more neurons are retained with increased environmental stimulation. Also, throughout life, “novel" input will add dendritic growth. It is possible that a thicker cortex may be protective against cortical degradative diseases such as Alzheimers ***(Diamond, 1985)***.

The lobes of the cerebral cortex are composed of gray matter and named for overlying cranial bones (Figure 1). The following is a description of the primary functions of each lobe ***(Sherwood, 2010).***

1- **Frontal Lobe** The frontal lobe contains one third of surface area of each hemisphere. It is the cortical area for planning ahead, decision-making, and speech. It also contains the primary motor cortex, which is located on the ridge (gyrus) anterior to the boundary involution (central sulcus). This area is in association with 3 other cortical areas in developing a “motor plan” for a specific voluntary task performed by contralateral muscle.

2- Parietal Lobe The parietal lobe is located posterior to central sulcus, and is the cortical area forabstract functions like mathematical calculations. It also contains the primary somatosensory cortex, for reception and processing of sensory information from the peripheral nervous system (touch, pain, balance, temperature).

3- Occipital Lobe The occipital lobe is located at back of cerebral cortex, behind the parietal lobe and is the cortical area where visual information is processed and visual capacity is that is needed to perform skills such as architecture.

4- Temporal Lobe The temporal lobe is located caudal to lateral fissure. The uppermost part is concerned with hearing.

5- Limbic Lobe The limbic lobe (limbus = edge, border”) is an arc of cortical and sub-cortical structures surrounding the brain stem and is located on the inner (medial) surface. It has a role in learning and memory processing in the hippocampus and is concerned with behavioral and emotional expression. There are specific regions designated as “reward” (pleasure) and “punishment” (unpleasant) centers.

B. Basal ganglia:

The inner core of sub-cortical structures is known as the basal ganglia. It consists of 4 discrete masses of neuronal bodies at base of each hemisphere: the amygdala, globus pallidus and the striatum with its sub-parts of the caudate nucleus and putamen. The caudate nucleus and putamen act as a great funneling system receiving fibers from virtually every portion of the cerebral cortex in precise topographic fashion and pass them on to the globus pallidus. From there, the fibers travel to the thalamus and brainstem nuclei. By these pathways, basal ganglia carry out their responsibility for the following effects:

1. Inhibit muscle tone through-out body
2. Selecting and maintaining purposeful motor activity while suppressing useless or unwanted patterns of movement.

(Diamond, 1985)

C. Diencephalon (Upper brain stem)

The diencephalon is divisible into four major parts: the epithalamus, the thalamus, hypothalamus and subthalmus. The epithalamus includes the pineal gland as well as three other structures. The thalamus or "inner chamber" is located at the base of the cerebral hemispheres on each side of the third ventricle. The hypothalamus - "under thalamus" is very small, weighing only 4 gms (< 1% of brain weight), but without peer in authority over body adjustments to our external and internal environment.

D. Pineal gland

The pineal gland is probably best known for its synthesis of melatonin from serotonin, by the actions of two enzymes sensitive to variations of diurnal light, Nacetyltransferase, and hydroxyindole-o-methyltransferase. Daily fluctuations in melatonin synthesis are rhythmic and directly related to the daily cycle of photic input. Light entrains the circadian rhythm to the environmental light cycle and also acts by an unidentified pathway to rapidly block the transmission of neural signal to the pineal gland. N-acetyltransferase activity is elevated during the night, but exposure to light turns off the enzyme activity. The exposure to constant light turns off this daily rhythm. The pineal gland acts as a neuroendocrine transducer, converting neural signals into an endocrine output, melatonin. This allows the pineal gland to function as a biological clock, delivering signals that regulate both physiological and behavioral processes. Fluctuations, called circadian rhythms, have a period of exactly 24 hours in the presence of environmental cues, while in the absence of such cues they only approximate the 24-hour cycle ***(Carpenter, 2004).***

E. Thalamus

The thalamus is the primary processing station for all sensory pathways (except olfactory) on their way to cortex. It is a relay station, like an electrical “junction box", to screen insignificant signals and route important signals.

F. Hypothalalmus

The hypothalamus has several very important regulatory junctions, it accomplishes by the secretion of neurohormones:

1. Released by neurosecretory neurons, that respond to and conduct action potentials like other neurons, but instead of being in close proximity to target cell, release their chemical messenger into blood vessel (portal system) upon appropriate stimulation.
2. Connected through portal system to master endocrine gland “pituitary" (hypophysis) located at the base of the brain.
3. Senses and controls osmotic balance (vasopressin release) in response to ECF solute concentrations, stimulating thirst and/or urine retention or output.
4. Regulates body temperature, metabolic rate and food intake.
5. Involved in emotional and behavior patterns Protection and Nourishment of the CNS Cranial meninges There are three connective tissue meninges (membranes) covering the brain, that offer support and protection to the CNS and provide a space for the circulation of cerebrospinal fluid.

G.1: The outermost, tough elastic membrane covering the brain is known as the Dura marer, or “hard mother" has middle meningeal artery along outer surface under the temporal bone-if hit on side of head, can rupture blood vessel and cause