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## Hypothermia as a treatment option for hypoxic-ischemic encephalopathy in newborns – A literature review

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**ABSTRACT**

**Introduction and purpose:** Neonatal asphyxia is a medical condition in which the neonate is not able to maintain sufficient respiratory function. The hypoxia may be caused by either an impaired respiratory activity of the neonate or an interruption of blood flow to the placenta in the period immediately before or during delivery, which resulted in inadequate oxygen perfusion to vital organs.

**Description of the state of knowledge:** Hypoxic-ischaemic encephalopathy (HIE) is a form of perinatal hypoxia, occurring in newborns after the 35th week of gestation and presenting along with neurological disorders. In fact, it is a major cause of death and infant disability. The incidence of HIE is approximately 2-5 per 1000 live births. The standard recommended treatment for perinatal hypoxic-ischaemic encephalopathy is therapeutic hypothermia. There are two methods used: selective head cooling with moderate whole-body hypothermia (SHC) and whole-body hypothermia (WBC). In both cases, metabolism and neural tissue destruction are slowed down.

**Conclusions:** Therapeutic hypothermia is a promising treatment option for neonatal encephalopathy. Thus, it decreases the risk of death and neurological deficits in the form of cerebral palsy, epilepsy and psychomotor retardation. Whole-body hypothermia appears to be a more successful method than selective head cooling, however more research is still needed.

**Key words:** hypothermia; treatment; newborn; hypoxic-ischemic encephalopathy

**INTRODUCTION**

Perinatal hypoxia called asphyxia is one of the most prevalent causes of perinatal death and the most important reason for neurological disorders in later life. This affects the whole body, with the central nervous system being the most vulnerable.[1] In contrast, hypoxic-ischaemic encephalopathy (HIE) is a form of perinatal hypoxia present in neonates after the 35th week of pregnancy, occurring with neurological disorders. It is a major cause of death and disability in children. The incidence of HIE is estimated to be approximately 2-5/1000 live births. [2],[3]

The risk factors for asphyxia include prematurity, birth-related factors, maternal disease, pathology of the fetus, placental and umbilical cord pathology. [1]

Therapeutic hypothermia is a treatment option for neonatal encephalopathy. It reduces the risk of death and neurological deficits in the form of cerebral palsy, epilepsy and psychomotor retardation. [4]

## **NEWBORN RESUSCITATION**

In neonates born with asphyxia, resuscitation plays a crucial role in preventing progressive hypoxic damage. The postnatal transition of the respiratory and cardiovascular systems requires cord clamping and lung aeration, so necessary steps such as providing warmth, clearing the airway, drying and stimulating by rubbing the infant's back are considered to be initial procedures. Term or preterm infants requiring positive pressure, due to lack of response to first-line procedures, should be exposed to air through ventilation, which needs to be started 1 minute after birth.

The initial assessment may occur before the umbilical cord is clamped and cut. [11]

Typically performed in this order:

- Tactile stimulation of newborn's feet or chest
- Observation of skin color
- Assessment of the pace, depth and symmetry of the respiratory track
- Heart rate assessment
- Checking the temperature

Assessment of the above parameters should take approximately 60 seconds and is used to establish a baseline, determine the need for support and / or resuscitation, and the appropriateness and duration of delayed cord clamping. If required, cardiopulmonary resuscitation should be undertaken until the newborn is stabilized.

Following resuscitation, induction of hypothermia down to 33–34 ° C should be considered in situations where there is clinical and / or biochemical evidence of a significant risk of moderate to severe ischemic encephalopathy. [12]

## **THE MECHANISM OF ACTION OF HYPOTHERMIA**

In severe hypoxia, cellular oxygen metabolism is disturbed, leading to depolarization of neurons and ischemia. The ischaemia, in turn, causes a cascade of disorders, ranging from a reduction in the availability of glucose needed for anaerobic metabolism to cell apoptosis. [5] The mechanism of therapeutic hypothermia causes a neuroprotective effect on the brain. This occurs by slowing down the metabolism of the neural tissue of the brain, resulting in a reduced glucose and oxygen demand. Neuron metabolism is reduced by 6-10% for every 1°C reduction, leading to a reduction in the release of excitatory amino acids and free radicals. And lowering the temperature to 32°C reduces the demand for oxygen and the production of carbon dioxide drops to 50-65% compared to normal. This requires adjusting the ventilation parameters of newborns with HIE to prevent hyperventilation. Frequent blood gas monitoring is necessary, especially in the early stages of treatment. [6]

## **TREATMENT METHODS**

Currently, two methods of cooling are available. The first is selective head cooling (SHC) by means of a cool cup - a special cap and consists in cooling the head to a maximum of 34-35°C. The temperature of the brain surface i.e., only the cerebral cortex, is being lowered. The second method is whole body cooling (WBC) obtained by means of a "cooling blanket". The newborn is placed in a deactivated, i.e. unheated incubator on a cooling blanket, in which the temperature of the flowing liquid is regulated by a thermostat, with the temperature setting at 25-30°C. This method cools various parts of the brain evenly and reaches deep structures - the base ganglia and hill. [6], [7]

The duration of hypothermia is 72 hours. Available data from studies conducted on pig neonates indicate that the temperature difference at SHC may be > 6 ° C between the surface of the cerebral cortex and the warmest areas of the deeper structures of the brain, while for WBC a temperature difference of <0.6 ° C was found. During therapeutic hypothermia in newborns, we use sedation and anticonvulsants, because pain, stress and prolonged convulsions may negatively affect and eliminate the neuroprotective effects of therapeutic hypothermia. [6]

## **CLASSIFICATION FOR TREATMENT**

Time in therapeutic hypothermia is extremely important because there is a therapeutic window that lasts from 1 minute to 6 hours of a newborn's life. In order to start treatment, a newborn baby must fit within the therapeutic window and must be classified under 2 main aspects. [7]

Firstly, neonates born in or above the 36th week of gestation and with at least one of the following criteria are eligible for hypothermia treatment:

1. Apgar Score of less than or equal to 5 at 10 minutes of life.
2. Need to continue resuscitation (artificial ventilation) at 10 minutes of age.
3. Acidosis in the first 60 minutes of life (defined as umbilical cord, arterial, or capillary pH of 7 or less).
4. A base deficit of greater than or equal to 16 mmol/L in umbilical cord or arterial, venous or capillary blood within the first 60 minutes of life.

If the neonate meets the above-mentioned criteria, a neurological evaluation is performed by using the Sarnat-Sarnat scale.

There are 3 forms: mild, moderate and severe. Diagnostic criteria include muscle tone, state of consciousness, seizures, body position, Moro and grip reflex, presence of suction, quality of breathing and pulse, appearance of fontanellas and pupils. [6]

Tab 1. *Hypoxic-ischemic encephalopathy scale (modified by Sarnat and Sarnat)* [10]

Assessment criteria	Encephalopathy severity				Hours from birth					
	Normal (N)	Mild (Mild)	Moderate (Mod)	Severe (S)	1h	2h	3h	4h	5h	6h
					:	:	:	:	:	:
<b>Level of consciousness</b>	Alert/arouses appropriately	Hyperalert	Lethargic	Stupor or coma						
<b>Spontaneous activity</b>	Normal	Normal or increased	Decreased	None						
<b>Posture</b>	Normal	Normal or mild distal flexion	Distal flexion, complete extension	Decerebrate						
<b>Tone*</b>	Normal	Normal or increased in trunk and extremities	Hypotonia (focal or general)	Flaccid						
<b>Suck reflex</b>	Normal	Normal or incomplete	Weak	Absent						
<b>Moro reflex</b>	Strong	Strong, low threshold	Incomplete	Absent						
<b>Autonomic system</b>	Pupils equal and reacting to light; normal heart rate and respirations	Pupils equal and reacting to light; tachycardia; normal respirations	Pupils constricted; bradycardia or periodic/irregular breathing	Pupils deviated/dilated/non-reactive; variable heart rate or apnoea						
<b>Seizures</b>	None	None	Common, focal or multifocal	Uncommon (excluding decerebration)						

\*Assess tone in both limbs and trunk/neck—presence of hypotonia in either meets the criteria.

Patients qualified for therapeutic hypothermia treatment need to undergo a brain MRI between 5 and 14 days of life, as hypoxic changes may not be visible on MRI between 24 and 48 hours of life. [8]

## REWARMING BABY

After 72 hours of cooling, the child needs to be warmed no faster than 0.5°C for 2 hours. The recovery time to normothermia is 12 to 16 hours. The temperature should be measured with a rectal probe. The target rectal temperature of the newborn baby is 37°C for at least 6 hours. The condition of the child should be monitored during the heating, as rebound hyperthermia, seizures or drops in blood pressure may occur with moderate to severe HIE, which is dangerous to the health of the child. [10]

## CONTRAINDICATIONS

The contraindications for hypothermia treatment include:

- severe head injuries,
- intracranial bleeding,
- head circumference less than 2 standard deviations (SD) for the gestational age with body weight over 2 SD,
- severe malformations and chromosomal abnormalities,
- critical prognosis, body weight less than 1800g
- age of a newborn with hypoxic-ischemic encephalopathy above 6h or no test results before 6h.

Attention should be paid to cardiac and respiratory disturbances, since therapeutic hypothermia may cause transient haemodynamic disturbances. [6]

## CONCLUSIONS

The incidence and severity of neurological and neurodevelopmental long-term sequelae depend on the seriousness of the hypoxic-ischaemic encephalopathy. The outcome of therapeutic hypothermia is a decrease of the mortality rate from 35% to 27% and a decrease of the neurological deficit from 48% to 27%. [9] Therapeutic hypothermia reduces the risk of death and alleviates severe neurological disorders as well as providing a viable opportunity to improve children's prognosis, such as cerebral palsy, cognitive development and psychomotor retardation. Whole-body hypothermia appears to be a better method than selective head cooling, but more research is needed. However, it is important to remember that although hypothermia is a promising and reducing treatment for HIE, still approximately 40 - 50% of children treated with hypothermia either die or will be severely disabled.[6]

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