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THERAPEUTIC HYPOTHERMIA OF NEWBORNS: RECOMMENDATIONS OF UNIVERSITÄTSKLINIKUM CARL-GUSTAV-CARUS (DRESDEN, GERMANY)

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Summary

Therapeutic hypothermia (TH) is a modern standard of care for newborns with gestational age ≥36 weeks who have moderate to severe hypoxic-ischemic encephalopathy. The introduction of TH is based on evidence-based medicine, and multiple randomized controlled trials confirm its efficiency in significantly reducing the risk of death or severe infant disability. Recent practice emphasizes the vital importance of clearly defined protocols for TH and its use in neonatal care settings with facilities for multidisciplinary care and adequate resources for comprehensive monitoring and treatment.

The article reports on the local protocol of TH in the neonatal intensive care unit of the University Hospital at Carl-Gustav-Carus at the Technical University Dresden (Dresden, Germany). TH is administered to newborns with moderate or severe hypoxic-ischemic encephalopathy who were born at a gestational age of ≥ 36+0 weeks, are less than 6 hours old and have no signs of massive intracranial hemorrhage. Exclusion criteria are threat to life, congenital malformations, severe intracranial hemorrhage and poor prognosis. Whole-body cooling to an internal body temperature of 33.5°C is preferred. The cooling period is 72 hours, with warming at a rate of 0.2°C per hour, followed by normothermia over the next 48 hours.

Comprehensive assessment of the infant's status includes the Thompson score, amplitude and standard electroencephalography, magnetic resonance imaging, control of blood coagulation, acid-base status and blood gases, etc. Follow-up therapy is aimed at providing adequate ventilatory support to prevent hypocapnia, sufficient fluid supply, effective analgesia and anticonvulsant therapy, etc. Emphasis is placed on the need for further cathemnestic monitoring of infants who underwent TH.

Key words: *Asphyxia at Birth; Hypoxic-ischemic Encephalopathy; Therapeutic hypothermia.*

Introduction

Perinatal asphyxia is a pathological state that is determined by the absence or acute limitation of oxygen supply to vitally important organs of the fetus/infant before, during, or immediately after birth. The etiologic factors of asphyxia are manifold and involve maternal comorbidities, placental pathologies, birth complications, gestational age more then 40 weeks, high birth weight, metabolic dysfunction, genetic or epigenetic malformations, perinatal infections, etc. As a consequence of impaired placental gas exchange, perinatal asphyxia can lead to hypoxia, hypercapnia and/or reduced perfusion of organs, including the brain, and the development of hypoxic-ischemic encephalopathy (HIE) [1, 24, 37, 40].

As of 2010, the International Liaison Committee on Resuscitation (ILCOR) guidelines require that newborns with moderate to severe HIE receive therapeutic hypothermia (TH), or cooling, for 72 hours, starting as soon as possible but at least within the first 6 hours after birth. At the moment, no new arguments have emerged to change this guideline [21, 34, 41].

Recent guidelines emphasize the crucial relevance of well-defined protocols for TH used in randomized controlled trials in high-income countries, including strict temperature control of 33-34°C for 72 hours. It is reasonable and safe to use TH in neonatal care facilities with multidisciplinary care and adequate resources for infusion therapy, respiratory support, pulse oximetry, antibiotic therapy, anticonvulsant therapy, and follow-up [7, 21, 34]. In resource-limited countries, TH is also recommended for the treatment of full-term or near-term infants (low-quality evidence), but professionals are cautious about the use of passive cooling and/or ice packs. So far, several studies of TH in low- and very low-income countries have been presented, showing conflicting results [17, 26, 34].

Lowering the body temperature to 33.5°C for 72 hours, started within the first 6 hours of life, reduces the risk of death or neurological damage in full-term infants with moderate to severe HIE [1, 40]. This effect was also reported in follow-up studies until the age of 6 years [22].

Progress notwithstanding, clinicians often face situations in the treatment of infants with HIE that are not clearly answered in existing guidelines or supported by adequate evidence from randomized controlled trials. For example, should late preterm infants with HIE be cooled? Is cooling beneficial

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for mild HIE? Is the therapeutic window optimal or could it be shortened or expanded? Would cooling to a higher or lower temperature be effective and safe? Can infection reduce the effectiveness of hypothermic neuroprotection? [10, 32].

Currently, there is no proof that TH is both effective and secure in late preterm infants [11, 32]. The latest recommendations of the American Association of Pediatrics define a gestational age of ≥ 35 0/7 weeks as the lowest appropriate gestational age for performing hypothermia. Internationally, a number of countries, including most European states, use a gestational age of ≥ 36 0/7 weeks as the lowest age appropriate for initiation of cooling. Currently, the NICHD Neonatal Research Network trial (NCT01793129) is ongoing to evaluate the safety and efficacy of whole-body hypothermia for 72 hours in late preterm infants with gestational age from 33 0/7 to 35 6/7 weeks and birth weight ≥1500 g at < 6 hours postpartum with moderate to severe HIE [31].

Recent studies suggest that neither longer duration nor lower temperature improves outcomes [32]. The present findings emphasize the importance of focusing on early initiation of TH within the first 6 hours of life, as there is no evidence of a positive effect of late cooling between 6 and 24 hours [13]. Deeper or prolonged cooling is not beneficial, and it is essential to follow established protocols for TH with a rectal temperature of 33.50C for 72 hours [3, 19, 36].

There is a lack of systematic proof that TH leads to improved neurodevelopmental outcomes, and there is no clear understanding of the risks and side effects for infants with mild HIE [6, 14, 30, 32]. In 2014, the Fetal Committee of the American Academy of Pediatrics presented guidelines for the use of TH in infants with mild to severe HIE, pointing out the likely beneficial effects for children with mild pathology. In 2021, the COOL PRIME trial was launched to assess the comparative efficiency of non-randomized cooling therapy versus normothermia in 500 infants from 12 locations, according to the PRIME inclusion criteria. The primary outcome is the Bailey Child Development Score at the age of two, with secondary outcomes including MRI data, duration of hospital stay, parental stress assessment, and standardized clinical examination [4].

The following guidelines provide a framework for the conduct of TH in the Neonatal and Pediatric Intensive Care Unit of the University Hospital Carl-Gustav-Carus (Dresden, Germany). The head of this department is Professor Mario Rüdiger, MD, who also heads the Saxon Center for Feto-Neonatal Health and is Vice President of the German Society of Perinatal Medicine. In addition, Prof. Rüdiger is the founder of the Deutsche Stiftung Kranke Neugeborene (DSKN), a charitable foundation whose main focus is to support research in the field of neonatal intensive care and psychological assistance to families whose children were born prematurely. It should be mentioned that thanks to the activities of the charitable foundation, support of German colleagues and citizens, two devices for mechanical ventilation and two devices for nCPAP were purchased for the neonatal units of the City Clinical Maternity Hospital No. 2 of the Chernivtsi City Council and the Chernivtsi Regional Perinatal Center of the Chernivtsi Regional Council. This modern equipment was also acquired for the Bukovinian State Medical University, which transferred it for joint use to these clinical bases. This will allow to improve the educational process of doctors of various specialties in the system of postgraduate education and continuing professional development at the Department of Pediatrics, Neonatology and Perinatal Medicine of BSMU (Fig. 1).

Figure 1. The device for carrying out the TH

As Prof. M. Rüidiger points out, not all the guidelines presented are "evidence-based" but are a compromise that ensures a unified procedure. This procedure is reviewed at regular intervals and adjusted when necessary.

Indications for TH

For every delivery, it should be checked whether there is any history for asphyxia (difficult delivery, resuscitation need etc.). In these infants signs for hypoxia/asphyxia should be checked, including pH of umbilical cord artery blood, arterial blood pH in the first 60 minutes of life, base deficite of arterial blood (Fig. 2). Every newborn delivered in a state of asphyxia is subjected to neurological examination.

If there are no signs of encephalopathy, the newborn should be observed clinically for at least 24 hours and with amplitude electroencephalography (aEEG) for up to several hours, and neurological observation should be performed.

Based on available data and ILCOR criteria, TH is indicated for neonates with mild to severe HIE who are born at ≥ 36+0 weeks' gestation, and are less than 6 hours old [12]. If such neonates have signs of both "asphyxia" and "encephalopathy," TH is initiated. Indications and initial steps are shown in Figure 2.

Exclusion criteria involve life-threatening symptoms, congenital anomalies, serious intracranial hemorrhage, and poor prognosis.

If the child is 6 to 24 hours old at the time of diagnosis, TH can also be considered.

The procedure of the TH

Cooling should be started immediately after the

indication – defining the signs. Preference should be given to whole-body cooling, at which the internal body temperature should be 33.5°C. The internal body temperature and the cooling/warming process could be controlled by servo control mechanism of the device, however, not all devices are equipped with a servo-control mode. As well as measuring the temperature with a device (e.g. CritiCool), the body temperature should be displayed on a monitor. Once the target temperature is reached, the warning limits of 33°C and 34°C must be set on the monitor. Clinical team should focus on keeping the temperature within that range.

The duration of cooling is 72 hours, and earlier discontinuation may be considered in cases of severe pulmonary hypertension with oxygenation disorders, massive intracranial hemorrhage, poor prognosis, or other serious side effects [12]. Warming is performed at a rate of 0.2°C per hour. After warming, it is necessary to ensure normothermia for the next 48 hours, avoiding hyperthermia during this stage [18].

Diagnosis

1. Clinical examinations

The Thompson score [39] is a clinical assessment tool that, by contrast to the Sarnat-Sarnat categorical rating system [33], enables a gradual assessment of severity. The score should be recorded initially in order to define severity of HIE (e.g. before cooling and without analgesia), and then every 24 hours until day 5 of life and after leaving the intensive care unit. A maximum score of 11 is associated with a very good prognosis (cognitive-free survival, sensitivity 0.93, specificity 0.61), whereas a maximum score of ≥15 is associated with a less favorable neurological outcome (specificity 0.94) [23].

2. Sonogaphy

Before cooling, an indicative brain sonography is performed to exclude malformations or massive intracranial hemorrhage. On the 3rd and 5th day, extended neurosonography with additional special scans is performed. Impaired cerebral perfusion on the 3rd day of life is not a reason to changing the warming stage [9].

3. aEEG

AEEG is a simple and very reliable method of assessing prognosis. It is performed continuously but documented once per shift in the medical record with 1 photograph of a typical EEG sequence.

Mild aEEG changes at the onset of cooling are associated with a good neurological outcome, but if the aEEG remains abnormal for more than 48 hours, the neurological prognosis is quite poor [16, 35].

4. EEG.

If there have been no clinical indications for multichannel EEG in the course of the disease to date, multichannel EEG is performed in all patients on the 4th – 6th day after hypothermia. Further examination intervals are determined depending on the results obtained and the therapy received.

5. MRI

MRI makes it possible to draw further prognostic conclusions about the severity of cerebral damage. The most informative results can be obtained at the age of 3-6 days after the injury [37]. Essentially, the goal is to perform MRI on all patients after hypothermia treatment, i.e., on days 4-6.

6. Laboratory testing

Refer to the TH chart (Fig. 2) for the laboratory values noted before and during cooling. Pay special attention to platelet count and coagulation, which may need to be corrected.

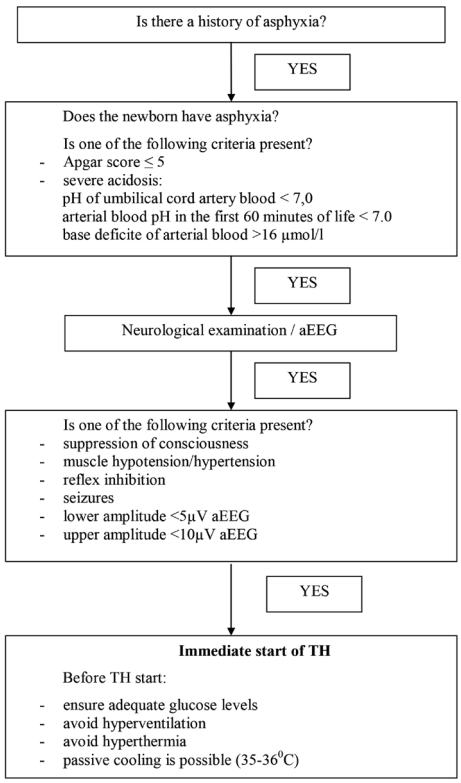

Fig. 2. Criteria for TH

Maintenance therapy

1. Respiratory support

Newborns with stable breathing can be left without respiratory support or on non-invasive respiratory support (CPAP, high-flow). Neonates who initially require mechanical respiration usually recover quickly, but in the first few hours of life they show a distinct tendency to hyperventilate with a risk of hypocapnia. Hypocapnia leads to cerebral vasoconstriction and thus to reduced perfusion. Studies have shown that hypocapnia is associated with an increased incidence of cerebral palsy and disability [15]. Since hyperoxemia in the first few hours after a hypoxic stroke also exacerbates cerebral damage, especially in association with hypocapnia, blood gases should also be carefully monitored in addition to SpO2 and pCO2 monitoring devices.

In the case of invasive ventilation, normoventilation should be achieved. The pCO2 value should be maintained without temperature correction in the range of 5.8-7.0 kPa (at 37°C), which corresponds to 4.8-6.0 kPa at 33.5°C. If patients undergoing invasive ventilation have severe tachypnea that usually persists until metabolic acidosis is relieved, extubation should be considered. If tachypnea is exacerbated by stress or anxiety, analgesia should be intensified.

Hypocapnia due to hyperventilation in spontaneously breathing pediatric patients can also be tolerated if there are insufficient data and no meaningful alternatives.

When administering oxygen, the saturation limits (92-96%) established in the department should be followed. In the case of additional oxygen support,

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the paO2 value should be kept in mind; paO2 > 12 kPa (10 kPa at 33.5 °C) should be avoided.

Persistent pulmonary hypertension can be treated and is not a contraindication to TH [12]. If pulmonary hypertension cannot be controlled therapeutically, discontinuation of cooling may be considered.

2. Painkillers

In clinical trials, only 50% of patients needed painkillers. In our department, morphine is immediately administered so that children undergoing treatment do not feel pain. In addition, the neuroprotective effect of morphine is postulated [25]. Stressful conditions should be avoided, as they can negatively affect the therapeutic outcome.

Morphine therapy is started with a bolus injection (0.1-0.2 mg/kg during ventilation, 0.05-0.1 mg/kg during independent breathing), and then maintained as a continuous infusion. Based on recent experience, almost all patients have to start with a minimum dose of 10 µg/kg/h. To achieve satisfactory analgesia, additional bolus doses and a temporary increase in the dose to 25 µg/kg/h are usually necessary. It should be noted that cooling reduces the morphine breakdown and thus prolongs the effect. Therefore, a slow decrease in the dose of morphine should be started on the first day of life, when the patient has received satisfactory sedation for several hours.

In neonates with critical ventilation, additional sedation with midazolam is usually necessary. If required, another opiate may also be used initially or later.

3. Anticonvulsant therapy

Seizures are considered to be related to poor neurological prognosis [27]. Both electroencephalographic and clinical seizures necessitate anticonvulsant therapy. In the department, levetiracetam (30 mg/kg, IV bolus) is the first choice drug [29]. If this does not lead to the cessation of seizure activity, this dose can be repeated. If there is no response, phenobarbital (20 mg/kg, IV) is administered. In many other institutions, phenobarbital represents the first line of anti-convulsive therapy. In case of prolonged sedation, midazolam therapy can be tried in bolus doses (0.1-0.2 mg/kg).

4. Diuresis support

Renal involvement is common in asphyxia. Although there is no evidence that furosemide improves renal function in asphyxiated patients, early bolus theophylline (8 mg/kg) improves urine output after asphyxiation. As a similar positive effect has also been described with a dose of 5 mg/kg theophylline [28], the lower dose is now administered as a preventive measure.

5. Nutrition/volume of intake

Early enteral nutrition is also advisable in hypothermia, but with a reduced amount of food, because, on the one hand, metabolism is significantly reduced, and on the other hand, intestinal perfusion is also limited. An increase in the incidence of NEC with low enteral nutrition in hypothermia has not been described [5].

We start on the first day of life with 5 ml of expressed breast milk or formula 6 times a day. Increasing the dose by 5 ml/day x 6 should be done when well tolerated, so that at the end of the cooling down period at 72 hours of age, the dose is 15 ml x 6. Optimally, half the amount of food should be administered at the end of the cooling stage. When warming up, the amount of food can be quickly increased. In this type of enteral nutrition, an additional glucose infusion is sufficient. Care should be taken to ensure adequate fluid intake (starting at 60-70 ml/kg, increasing to approximately 120 ml/kg on day 4) in these patients; fluid restriction should be avoided as it is associated with increased mortality and poor neurological prognosis [38].

6. Metabolism.

Adequate glucose intake (starting at 7 g/kg/day if there is no initial hyperglycemia) should be provided with strict control of blood glucose levels, as anaerobic metabolism requires more substrate for energy production, and transient hyperinsulinism can also be observed after perinatal asphyxia [2].

In case of initial hyperglycemia, glucose intake should be reduced for several hours (at least 5 g/kg/day). Insulin administration is usually not required, and this increases the risk of hypoglycemia.

7. Monitoring

Body temperature should be maintained as constant as possible at 33.5°C. Fluctuations in temperature should be avoided. During hypothermia, the heart rate is usually low, so the limits are set at 70-140 beats per minute.

It is necessary to closely monitor the level of electrolytes and blood glucose (Fig. 2). Attention should be paid to a possible electrolyte imbalance in the presence of inadequate antidiuretic hormone secretion and acute renal tubular necrosis due to severe asphyxia. Hypocalcemia (ionized < 1.0 mmol/L) and hypomagnesemia reduce the seizure threshold and should be corrected.

8. Acid-base balance

When the body temperature decreases, the solubility of blood gases increases and the partial pressure of CO2 decreases. It decreases by 0.3 kPa per 1°C decrease, the pH value increases by 0.015 per 1°C. Depending on the method of measurement, it should be specified in each department at what temperature values are measured in order to have comparable values. If blood gases are measured at 37°C (alpha-stat method), the target range for CO2 should be 5.8-7.0 kPa for 37°C (equivalent to 4.8-6.0 kPa at 33.5°C in the patient).

Side effects

At body temperatures below 35°C, the heart rate drops by about 10 beats per minute for every 1°C decrease in temperature. Since the basal metabolic rate decreases by about 8% per 1°C, the reduced cardiac output meets the need. Hypothermia-induced bradycardia is a physiologic response and does not require therapy.

There is a risk of hypokalemia during the hypothermia induction stage, but hyperkalemia can occur during the warm-up phase.

The risk of hemorrhage is increased in hypothermia as a result of the negative effect on plasma coagulation. Platelet function and number are often reduced. Therefore, in case of pathological plasma coagulation, fresh plasma and vitamin K should be replaced with IV, platelets should be above 80 G/L. It is necessary to control clinical signs of bleeding.

Hypothermia affects the pharmacokinetics and dynamics of drugs, this is true for morphine, fentanyl,

midazolam, phenobarbital, vecuronium, etc. [8, 20].

Further steps

The risk of neurologic damage remains high despite administration of hypothermia, and is 35% in infants with mild HIE and 63% in infants with severe HIE. Therefore, adequate follow-up care is necessary.

1. Rehabilitation

All newborns with HIE should receive rehabilitation care – if possible. The aim is an early transfer to rehabilitation treatment on days 6-10. Parents should receive an appropriate information about the next steps.

2. Outpatient care

Structured outpatient follow-up should be provided for children aged 3, 6, and 12 months at the developmental outpatient clinic. At the age of 24 months, children receive a standardized neurological examination according to Bayley III.

Conclusions

1. Therapeutic hypothermia is a current standard of care supported by evidence-based medicine for neonates with gestational age ≥36 weeks and mild to severe HIE. Multiple randomized controlled trials have shown that TH reliably reduces the risk of death or severe disability in children of this cohort.

2. Current standards emphasize the critical importance of well-defined protocols for TH, including initiation within the first 6 hours of life and strict temperature control of 33-34°C for 72 hours. It is safe to provide TH in neonatal care facilities with multidisciplinary care and adequate resources for comprehensive monitoring and treatment.

3. Despite the advances, clinicians often face situations in the treatment of neonates with HIE that are not clearly defined in current clinical practice guidelines or supported by sufficient evidence from randomized controlled trials. Questions remain about the efficacy and safety of TH in preterm infants and neonates with mild HIE and sepsis, changes in the therapeutic window and target temperature, etc.

4. The article introduces the local protocol for therapeutic hypothermia in the neonatal intensive care unit of the University Hospital at Carl Gustav Carus (Dresden, Germany). These guidelines are a compromise that provides a unified procedure and are verified at regular intervals and adjusted accordingly if needed.

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ЛІКУВАЛЬНА ГІПОТЕРМІЯ НОВОНАРОДЖЕНИХ: РЕКОМЕНДАЦІЇ UNIVERSITÄ TS KLINIKUM CARL GUSTAV CARUS (М. ДРЕЗДЕН, НІМЕЧЧИНА)

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Резюме

Лікувальна гіпотермія (ЛГ) – сучасний стандарт допомоги новонародженим дітям з терміном гестації ≥36 тижнів, які мають прояви помірної та важкої гіпоксично-ішемічної енцефалопатії. Впровадження ЛГ засновано на даних доказової медицини, а чисельні рандомізовані контрольовані дослідження підтверджують її ефективність у достовірному зниженні ризику смерті або тяжкої інвалідності дітей. Сучасні рекомендації наголошують на критичній важливості чітко визначених протоколів проведення ЛГ та її застосування у закладах неонатальної допомоги з можливостями мультидисциплінарного догляду та наявності відповідних ресурсів для проведення комплексного моніторингу та лікування.

У статті представлено локальний протокол проведення ЛГ у відділенні неонатальної інтенсивної терапії університетської клініки Карла Густава Каруса Технічного університету Дрездена (м. Дрезден, Німеччина). ЛГ проводиться новонародженим з проявами помірної або тяжкої гіпоксично-ішемічної енцефалопатії, які народилися при терміні гестації ≥ 36+0 тижнів, мають вік менше 6 годин і не мають ознак значного внутрішньочерепного крововиливу. Критеріями виключення є загроза життю, вроджені вади розвитку, значний внутрішньочерепний крововилив та поганий прогноз. Перевага надається охолодженню всього тіла до внутрішньої температури тіла дитини 33,5°С. Тривалість охолодження становить 72 години, зігрівання проводиться зі швидкістю 0,2°С на годину, після чого забезпечується нормотермія протягом наступних 48 годин.

Комплексний моніторинг стану дитини включає оцінку за шкалою Томпсона, проведення амплітудної та стандартної електроенцефалографії, магнітно-резонансної томографії, контроль показників коагуляції крові, кислотно-лужного стану та газів крові тощо. Підтримуюча терапія спрямована на забезпечення адекватної вентиляційної підтримки з уникненням гіпокапнії, достатнього рідинного навантаження, ефективного знеболення та протисудомної терапії тощо. Акцентована увага на необхідності проведення подальшого катамнестичного спостереження за дітьми, яким була проведена ЛГ.

Ключові слова: асфіксія при народженні; гіпоксично-ішемічна енцефалопатія; лікувальна гіпотермія.

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