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PRACTICAL ASPECTS OF THERAPEUTIC HYPOTHERMIA IN NEONATES WITH HYPOXIC ISCHEMIC ENCEPHALOPATHY – QUESTIONS AND ANSWERS. PART I. PROVIDING NEWBORN CARE BEFORE AND DURING TRANSFER TO THE REFERENCE CENTER*

PRAKTYCZNE ASPEKTY HIPOTERMII LECZNICZEJ W ENCEFALOPATII NIEDOTLENIOWO-NIEDOKRWIENNEJ NOWORODKÓW – PYTANIA I ODPOWIEDZI. CZĘŚĆ I. PRZYGOTOWANIE DO TRANSPORTU I TRANSPORT DO OŚRODKA REFERENCYJNEGO

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Abstract

The first decade of the 21st century saw the worldwide spread of therapeutic hypothermia as a beneficial therapeutic procedure in neonates with hypoxic-ischemic encephalopathy. New guidelines for the resuscitation of newborns confirm that therapeutic hypothermia should be the standard method of treatment offered to neonates with acute perinatal hypoxia. The quality of care which an asphyxiated newborn receives during and immediately after resuscitation, as well as the mode of preparation for transport, can have a significant impact on improving the outcome, but it can also result in the deterioration of neonates treated with hypothermia. Since to a considerable degree the therapeutic effect depends on the time of beginning the cooling procedure, there is no reason to unnecessarily delay treatment. For this purpose, neonatologists or pediatricians from referring hospitals who do not have the equipment for hypothermia can and even should begin the cooling process while waiting for the arrival of the neonatal transport team. In that short period a number of concerns arise regarding the optimal methods of child care and preparation for transport to the hypothermia center. The authors discuss the possibility of initiating cooling before transportation using simple, so called low-tech cooling methods, the possible risks associated with the incidence of hyperthermia, difficulties in the interpretation of the eligibility criteria, supportive therapy, and the problems connected with the communication process between the medical team and the parents. The aspects that have been analyzed should be helpful for professionals in neonatal wards, outside hypothermia centers.

Key words: newborn, hypoxic-ischemic encephalopathy, induced hypothermia

Streszczenie

Pierwsza dekada XXI wieku to okres upowszechniania na świecie hipotermii leczniczej jako efektywnej procedury terapeutycznej u noworodków z encefalopatią niedotlenieniowo-niedokrwinną. Nowe wytyczne z zakresu resuscytacji noworodka potwierdzają, iż hipotermia lecznicza powinna być standardową metodą leczenia oferowaną noworodkom z przebyłym ostrym niedotlenieniem okołoporodowym. Jakość opieki, którą otrzymuje noworodek w trakcie i bezpośrednio po resuscytacji

oraz sposób przygotowania go do transportu mogą mieć istotny wpływ na poprawę, ale mogą też skutkować pogorszeniem wyników leczenia noworodków poddanych hipotermii. Ponieważ efekt terapeutyczny w dużej mierze zależy od szybkości rozpoczęcia procedury chłodzenia, nie ma powodu dla niepotrzebnego opóźnienia leczenia. W tym celu, neonatolodzy lub pediatrzy z ośrodków nie dysponujących aparaturą do hipotermii mogą i wręcz powinni, rozpocząć proces chłodzenia podczas oczekiwania na przyjazd zespołu transportu neonatologicznego. W tym krótkim okresie pojawia się szereg wątpliwości dotyczących optymalnych metod opieki i przygotowania dziecka do transportu do ośrodka hipotermii. Autorzy omawiają możliwości rozpoczęcia chłodzenia jeszcze przed transportem, niezaawansowane metody chłodzenia tzw. „low-tech”, ewentualne ryzyko związane z występowaniem hipertermii, trudności w interpretacji kryteriów kwalifikacji, leczenie wspomagające oraz problemy związane z procesem komunikacji pomiędzy zespołem medycznym i rodzicami dziecka. Poruszane aspekty powinny być pomocne dla lekarzy dyżurujących w oddziałach noworodkowych, poza ośrodkami hipotermii.

Słowa kluczowe: noworodki, encefalopatia niedotlenieniowo-niedokrwienne, hipotermia indukowana

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The first decade of the 21st century saw a worldwide spread of therapeutic hypothermia as a procedure in hypoxic-ischemic encephalopathy. New guidelines for the resuscitation of newborns published in 2010 by the *Academy of Pediatrics*, the American Heart Association and the European Resuscitation Council confirmed that therapeutic hypothermia should be a standard treatment method provided to newborns after acute birth asphyxia. Taking into account the pathophysiology of changes in the central nervous system and the relatively short, so-called therapeutic window, which on average lasts about 6 hours, it is crucial to make prompt and right decisions in this period, which is difficult for both the parents and for the babies [1]. The quality of care provided to newborns during and immediately after resuscitation, as well as the methods of preparing for transfer can have a significant impact on improving the final outcome, but they can also result in worsening the treatment results in newborns after therapeutic hypothermia. The first years of applying hypothermia proved that the controlled lowering of newborn core temperature is safe and possible adverse events are clinically insignificant, transient and do not result in lasting sequelae. Since the outcome of the treatment to a large extent depends on how swiftly the cooling procedure is applied, there is no reason for any unnecessary delay in initiating the treatment. Therefore, neonatologists or pediatricians, also those from the centers with no hypothermia equipment, can or even should commence the cooling process while waiting for the neonatal transportation team.

INITIATING THE COOLING PROCESS IN THE REFERRING HOSPITAL

Already in the 1990s, experimental research on animal models indicated that the swift initiation of the cooling process i.e. already at the beginning of the therapeutic

window, increases the neurons' chance of survival, and reversely, the later the procedure is commenced, the larger the number of dying neurons was observed (through the process of necrosis and apoptosis). Simultaneously, even slight changes to the temperature of newborns during the sentinel hypoxic-ischemic event proved to be able to critically affect the ultimate outcome. The results of both experimental and clinical research demonstrated that hypoxic-ischemic damage to the brain still progresses after the stage of resuscitation. What supports the need for initiating prompt cooling initiation are the results of experimental research on animals, where the application of even short-term hypothermia (i.e. for only an hour) but initiated directly after resuscitation, significantly reduced the number of dying neurons [2, 3].

However, many specialists have doubts about whether the cooling procedure should begin and whether not to wait for the recruitment criteria to be verified by specialists experienced in induced hypothermia. The definitive decision to refer the newborn to undergo the cooling procedure is typically made by a therapeutic team in therapeutic hypothermia centers. Observation shows, however, that it usually happens in the 5th-6th hour of the baby's life. The experience in hypothermia over recent years and cooperation with reference centers encourage decisions about the earlier initiation of cooling in the referring hospitals i.e. still prior to the arrival of the transportation team. This makes it possible to reach the target temperature faster, even in the 1st-1.5th hour of life. The first Polish multi-center study on therapeutic hypothermia demonstrated that in 75% of the patients who were transferred to hypothermia centers, passive (93%) or active cooling (7%) was initiated still in the referring center and 35% of the newborns reached the hypothermia center when their target core temperature had already been achieved. In almost 20% of the newborns, overcooling, defined as the core temperature $<32^{\circ}\text{C}$, was found.

The first therapeutic decision to be made, then, is to switch off the radiant heater during resuscitation instantly after the efficient ventilation and heart rate have been achieved. In physiological conditions the healthy, term newborn's temperature, which is typically 0.5°C higher than that of the patient in labor, drops to 36°C within 30 minutes. The asphyxiated newborn spontaneously cools down considerably faster, even to 34.5°C in 2 hours, which was demonstrated over 50 years ago. The phenomenon is referred to as natural hypothermia [4]. It is a rule that the more asphyxiated the newborn, the more intense the spontaneous cooling process.

While continuing the cooling process, one should remember to switch off heating and to reduce the temperature also in the transportation incubator during the transfer of the baby to the neonatal department. During this phase it is also extremely important to check deep temperature frequently enough. It is advisable to place a temperature detector at 6 cm in the rectum already in the first 20 minutes after birth [5]. This is usually the moment of the baby's being transported to the ward. Temperature should then be measured repeatedly and recorded every 15 minutes.

The target temperature range is another issue that raises doubts. Nowadays two standard methods of hypothermia are applied: Selective Head Cooling (SHC) with moderate cooling of the whole body, where the target temperature equals 34.5°C (the range from 34 to 35°C), and Whole Body Cooling with the temperature of 33.5°C (the range from 33 to 34°C) [6, 7]. Since during the preparation for transport, as well as during transportation, the whole newborn body is cooled, it is the temperatures applied in the WBC method that should be taken as the target cooling range. Unlike in the newborn warming phase, which completes the cooling process, there are no limits to the pace of achieving hypothermia. The sooner we reach the target temperature range, the sooner we obtain the neuroprotective effect and the less brain damage is done.

The next decision involves the choice of the method of cooling the newborn. Cooling can be performed in a passive way or by opting for active modes. Passive cooling can be sufficiently effective in many situations, particularly in lower temperatures of the environment and also in the case of acute asphyxia, when the process of natural endogenous hypothermia is more intense. However, whenever passive methods fail, or the prompt introduction of hypothermia is preferable, active cooling methods should be selected. Active cooling includes the application of cold gel packs. Plastic bags or even simple latex gloves filled with cold water (10-15°C) can also be utilized and placed along the newborn's trunk and neck, in the armpits and the groins, and on the newborn's head. The temperature applied on the newborn's body should be comparable to the temperature of the cooling caps and mattresses used in the standardized equipment for therapeutic hypothermia. In the SHC method, the temperature of the cooling cap ranges from 9 to 18°C, whereas in WBC the process commences with lower temperatures of the mattress, i.e. 28°C, and while controlling the deep temperature, the value is

gradually increased, so as to achieve the target range of a maximum of 32°C.

By initial application of a lower temperature (approx. 28°C) the target temperature is accessible within 25-35 minutes. There is no need to use frozen gel packs or ice bags in order to effectively cool down the newborn's body [8]. The application of excessively low temperatures on the skin may result in side effects, such as subcutaneous fat necrosis and may also lead to unnecessary overcooling. Incidents of overcooling have repeatedly been reported in publications [9, 10]. A newborn cooled down to 28°C during long transportation was also admitted to the clinic at the Polish Mother's Memorial Hospital. Moreover, in such a situation, it is vital to reach the target temperature gradually. Similarly to the warming phase, the temperature increase should not exceed 0.5°C per hour. In extreme cases of overcooling, the process of warming the newborn to the required temperature range applied in standard hypothermia, i.e. 34.5°C in the SHC method, can even amount to 12-13 hours.

There have been attempts to apply newborn hypothermia exclusively with so-called low-tech methods, which exploit the phenomenon of natural hypothermia. Such reports typically come from developing countries that have little or no access to more advanced, and thus costly, so-called high-tech methods. Such procedures are normally accompanied by cold infusions and relatively high doses of sedative drugs. Last year a paper published by Swiss authors from a pediatric intensive care unit also demonstrated the efficacy of such a method of cooling. However, the clinical course of the described group of patients, i.e. applying catecholamines and volume expanders twice as frequently, and the double mortality rate that has been reported (although statistically insignificant) do not provide adequate grounds for promoting this method whenever medical equipment in hypothermia centers is available. The authors did not provide long-term results, either, therefore there is no evidence of the safety of such a course of action [11].

THE RISK CONNECTED WITH HYPERTHERMIA

On the other hand, we should emphasize the adverse influence that hyperthermia has on the asphyxiated newborn. The hyperthermia effect has been proven to be particularly harmful in the first hour (15-45 minutes) after the phase of asphyxia. Following this period, its destructive impact is considerably milder. The results of clinical and animal model research confirmed that hyperthermia enhances the effects of hypoxic-ischemic injury to the brain [12-14]. This may result from caspase-3 activity in the execution phase of apoptosis (caspase-3), damage to the layer of pyramidal neurons (CA region) in the hippocampus, as well as from the disturbed balance of mineralocorticoid and glucocorticoid receptors largely located in the hippocampus, which is highly sensitive to hypoxia. Excessive activation of glucocorticoid receptors augments neurodegenerative processes, whereas the stimulation of mineralocorticoid receptors makes the survival of the neurons possible [15-17].

RECRUITING NEWBORNS FOR HYPOTHERMIA TREATMENT

Directly after resuscitation, the team responsible for the decision concerning the further treatment of the newborn should assess the baby's condition, the asphyxia grade and neurological risk, then contact a hypothermia center and a neonatal transport team. The decisions on newborn transfer must be taken very quickly. Neonatal transport must be launched immediately after the hypothermia center has been notified.

The assessment of the newborn's maturity is a significant issue among the recruitment criteria. As a standard, hypothermia is applied in newborns ≥ 36 week of gestational age. According to the criteria of guaranteed care provided and approved by the Polish Health Fund (NFZ), hypothermia in newborns after 35 weeks of gestational age was also accepted. The implementation of this method in more immature patients is currently being investigated in the world. The first results are cautiously interpreted and so far no clear evidence of the safety and efficiency of this method in such patients has been provided. Consequently, its application in the group of so-called late preterm babies (>32 weeks of gestation) should still be considered experimental.

INTERPRETING RECRUITMENT CRITERIA

When referring a newborn to the hypothermia program, doctors cannot be entirely sure whether the newborn will ultimately be recruited for hypothermia treatment. The literature available also reports that the verified criteria of cooling are met by about 75% of the neonates referred to hypothermia centers [18]. The newborns who are referred do not always fulfill the recruitment criteria defined in neurological assessment and EEG recording. Those who are typically evaluated as Grade 3 or Grade 2 in the Sarnat Grading Scale but with simultaneously occurring convulsions usually fulfill all the criteria. Neonates initially recruited as Grade 2 of encephalopathy without convulsions do not always demonstrate changes in the EEG recording. In such cases, the decision should always be made for the baby's benefit i.e. to recruit him/her for cooling. The interpretation of the EEG recording is more complicated, as it may be affected by the large doses of sedatives and anticonvulsants that had been administered. The Sarnat Scale, which is commonly used in patients' neurological assessment, also has its limitations: it was designed in the 1970s and used to assess asphyxiated newborns after 24 hours of life. Unfortunately, neurological evaluation and its registration in the form of standardized scales may still pose a serious problem for neonatologists.

ANTICONVULSANT TREATMENT OF ASPHYXIATED NEWBORNS

Neonates after asphyxia represent a group of patients who usually require the application of anticonvulsant medication. There are no indications for its preventive administration [19]. Phenobarbital can be administered

exclusively in newborns manifesting convulsions and 20 mg/kg of body weight is considered a loading dose. Higher and repeated doses cause a depression of the aEEG waveform. The administration of sedatives and anticonvulsants may lead to a rapid reduction of the newborn's core temperature. Keeping the mechanism in mind, in that period we should be particularly careful to control the newborn's core temperature.

Surprisingly, despite disturbing reports concerning the apoptotic and neurodegenerative action of phenobarbital, the methods of neonatal seizure treatment have largely remained unchanged for over 50 years.

The basic advantages of the drug include: its quick crossing of the blood-brain barrier, possible intravenous or intramuscular application and the possibility to continue oral treatment. Moreover, it has been proven that there is a good correlation between the serum level of the medication and the administered dosage. Its anticonvulsant effectiveness, however, is not very high and amounts to only 50%. It is an increasingly widespread opinion that the administration of phenobarbital in asphyxiated newborns should be avoided. Recently, it has been demonstrated that phenobarbital administered prior to the initiation of cooling (as prophylaxis or treatment) does not augment the



Fig. 1. An example of a simple method of active newborn cooling; latex gloves filled with cold water (approximately 15°C).

Ryc. 1. Przykład prostej metody aktywnego ochładzania noworodka – rękawice lateksowe wypełnione wodą o temp. ok. 15°C.

hypothermia effect but even leads to worse therapy outcome (higher death risk or the risk of alterations in MRI). As common practice shows, however, in many places, including Poland, phenobarbital still remains the first-line choice. Nonetheless, widespread research is being conducted today on the potential application of alternative anticonvulsant drugs [20]. Italian researchers have undertaken the efficacy assessment of topiramate – an anticonvulsant drug with additional neuroprotective properties which is applied parallel to hypothermia. However, the intravenous form of the drug is not available in the EU [21]. The authors from Upsalla represent another standpoint and begin anti-seizure treatment in asphyxiated neonates with the application of benzodiazepines (diazepam, midazolam) without making an attempt at phenobarbital therapy. As the second-line treatment then, a continuous infusion of lidocaine is applied (starting dose of 2 mg/kg, next an infusion of 6 mg/kg/h, or a continuous infusion of 4 mg/kg/h without a starting dose which may be increased up to 6-8 mg/kg/h within a maximum of 12 hours). The drug dosage is gradually reduced, so as to withdraw it within 1-3 days [22]. The effectiveness of lidocaine and midazolam as anti-seizure treatment in asphyxiated neonates has also been confirmed by researchers from Japan and Israel [23, 24].

New, promising options of anticonvulsant therapy include bumetanide, a loop diuretic which inhibits the Sodium-Potassium-Chloride Cotransporter NKCC1 and levetiracetam, which has excellent pharmacokinetic properties, high effectiveness and a good safety profile [20]. Both agents, however, fall into the category of drugs which have been poorly investigated in the neonatal period and their actual safety and effectiveness are yet to be proven by further research [25, 26].

SUPPORTIVE THERAPY

The aim of treating a newborn with hypoxic-ischemic encephalopathy is to maintain the normal values of such parameters as PaO₂, PCO₂, glycaemia and arterial blood pressure in order to prevent (or at least diminish) secondary damage to the central nervous system. One of the key aspects of the practice is the maintenance of normoglycemia. The biochemical change cascade that ensues from hypoxia and reperfusion (changes of neurotransmitters and the activity of their receptors) causes the cellular energetic processes to rely on the sufficient supply of glucose provided as a substrate. Glucose concentration in the brain is another factor determining the ultimate treatment outcome of newborns with hypoxic symptoms. Hence, the influence of both high and low glucose concentrations on the remote neurological results is equally interesting. This aspect of treatment happens to be omitted during the initial procedures of preparing the newborn for transport. In the neonatal intensive care unit, in turn, intravenous glucose infusions are routinely applied to patients, including asphyxiated neonates.

Multi-center research conducted in Ireland included 52 asphyxiated neonates and demonstrated a strong statistical correlation of early hypoglycemia occurring in the first 6 hours of life and defined as the glucose concentration <46.8 mg/dL (2.6 mmol/L) with a severe

form of HIE ($p=0.012$) [27]. Similar observations made by Salhab et al. also demonstrated a correlation between initial glucose concentrations <40mg/dL and neurological disturbances observed in the follow-up [28]. Worse results of neurodevelopmental care related to hypoglycemia in the first 24 hours of life were, moreover, reported by the authors from the UC San Francisco Medical Center who demonstrated that there is a 4.82-fold increase of the risk it will result in a 1-point lower psychomotor assessment ($p=0.038$) and the assessment of language and cognitive development can be even 15 points lower when measured according to the Bayley Scales of Infant Development ($p=0.0015$) [29]. However, all the above research was carried out before hypothermia was implemented. Only in the analysis by Tam et al., 11.5% of the study group were treated in the era of hypothermia but no observation indicating hypoglycemia was made in any of the newborns. It is, therefore, hard to extrapolate such results directly to the group of neonates currently treated with hypothermia. It should also be emphasized that substantial fluctuations of glycaemia are detected in asphyxiated newborns and they are linked to their serious condition. The most significant oscillations occur in the most severe form of HIE newborns, so the results in these patients are likely to be the most disturbing.

Hyperglycemia, in turn, does not only fail to prevent hypoxic alterations but it might also enhance them. Research on animals demonstrated that glucose administered even before the ischemic encephalopathy extended the morphological damage to the brain. In such conditions the mechanism of brain damage is likely to be connected with neuronal apoptosis which occurs after reperfusion with a high concentration of glucose substrate in the cells with ATP depletion. It was proven that hyperglycemia just after a hypoxic-ischemic event reduces the amount of ATP in the brain and oxygen absorption, simultaneously increasing vascular endothelial thickness and causing focal infarcts. Careful monitoring of glycaemia concentration is, therefore, necessary [31].

INFORMING THE NEWBORN'S PARENTS

Doubts during the conversation with parents

Giving the information to the neonate's parents may cause difficulties. Parents are usually startled by the course of delivery and unprepared for the information about the baby's bad condition. They may manifest a demanding attitude. An additional obstacle includes passing on the information that it is necessary to transfer the baby to another hospital, often dozens of kilometers away, the baby's separation from the mother and the probability of the baby's recruitment for "cold treatment", i.e. hypothermia. In the conversation, the following aspects of the transfer to a hypothermia center are worth pointing out:

- it is currently the best treatment method that can be provided after serious hypoxic-ischemic encephalopathy,
- the risk of complications arising from the therapy is low,
- the results of the treatment are better in comparison with conventional therapy,

- the procedure is comparable to ice application in sports injuries,
- the baby's core temperature is reduced merely by 2-4.5°C.

While agreeing to the baby's transport to another hospital and to treatment in a reference center, the parents should also sign a written consent form concerning the potential cooling procedure. The transport can allow time for the parents' phone contact with the reference hospital.

THE PATIENT'S MEDICAL RECORDS

Despite the necessity to act swiftly, medical records must be thoroughly compiled and accurately completed. It is extremely important for the documentation to include obstetric history, a description of the course of delivery and the first examination of the newborn. The patient's records should contain the following items:

- the procedures applied during resuscitation should be detailed according to the new, extended Apgar Scale; The scale has been recommended by the AAP and the American Society of Obstetrics and Gynecology since 2006 [33]; in Poland the requirement of longer assessment i.e. after 5 minutes of life is also imposed by the Minister of Health's Regulation of 20 September, 2012.
- additional test results, particularly umbilical cord blood (preferably arterial) gas analysis;
- records of the cooling process with specified time needed for the target temperature to be reached (core temp. measurement taken every 15-30 minutes);
- newborn neurological assessment according to the Sarnat Grading Scale (some centers prefer the Hamilton Scale);
- treatment description with medication doses and a careful specification of the time of their administration;
- the parents' consent for the baby' transfer, treatment in the intensive care unit and hypothermia therapy.

Negligent and inaccurate compilation of the documents may raise further doubts over neonatal procedures and can provide a legal basis for financial claims in case there is an investigation into potential malpractice and shortcomings in the procedures. Such situations are fairly common when neonates are born with sentinel perinatal events.

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