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Review

Establishing a hypothermia service for infants with suspected hypoxic–ischemic encephalopathy

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SUMMARY

The translation of new treatments based upon established evidence into clinical practice is often difficult. The establishment of a therapeutic hypothermia (TH) service and a related cooling register would provide the opportunity to examine how a new therapy becomes implemented in a country or region. The objectives of a TH program should be: to provide guidance to clinicians who are considering the introduction of this new therapy; to ensure standardized clinical practices; to audit the implementation and conduct of TH; to provide surveillance for cooling-related adverse effects; and to evaluate the subsequent neurodevelopmental outcome. Prior to the use of TH, the most important practices to prioritize during its implementation should be identified and include the following: ensure timely identification of infants with neonatal encephalopathy; develop a coordinated system with the local or regional referral cooling center; develop a transport team capable of performing cooling during transport; ensure that each participating unit has access to a national encephalopathy register, and have developmental follow-up arrangements in place that are appropriate and uniform for the region/country.

1. Introduction

The incidence of hypoxic–ischemic encephalopathy (HIE) is currently unclear, with estimates ranging from 1 to 8 per 1000 live births worldwide [1,2]. Approximately 15–20% of affected newborns die within the postnatal period, and 25% of those who survive develop severe childhood disabilities. Recent clinical trials have evaluated hypothermia as a neuroprotective intervention for HIE. A recent meta-analysis of these trials has demonstrated that therapeutic hypothermia (TH) significantly reduces mortality and neurodevelopmental disability [3]. Although reports from single institutions indicate that therapeutic hypothermia is increasingly used, there have been few reports of national and/or regional implementation of this therapy to date. Given that the incidence of moderate-to-severe HIE may affect 0.9 to 1.2 per 1000 live births, this could potentially affect between 720 and 960 infants out of the 800,000 annual births in France each year. The translation of a new treatment such as TH into clinical practice can be facilitated by providing consensual programs and by establishing registers that contain collective data that can be used to examine how the new therapy has been implemented and its effectiveness. In 2010, the French Neonatal Society published TH guidelines for hypoxia–ischemia neonatal encephalopathy (NE) [4]. In this study, our aim was to develop a nationwide consensus on practice guidelines consistent with the international standard protocols and compatible with the current perinatal organization system in France. In effect, we established a French National Cooling Register (SFN-R). At the same time, a population-based Regional Register (Center of France Register CF-R) was implemented in the Center of France Region in coordination with the national organization and the regional perinatal network.

2. Implementation of an evidence-based protocol for TH

2.1. Coordination and training programs

Prior to the implementation of TH, it is important to develop a system of coordination with referring hospitals in order to ensure that TH is available for eligible infants within 6 h of birth. It is also important to provide the perinatal healthcare teams with training

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and educational resources. This coordinated system of care and healthcare worker training should rely upon the regional perinatal network organization consisting of midwifes, obstetricians, and neonatologists. A representative parent should participate in the establishment of the TH program, particularly in determining the follow-up procedures. The critical challenge in implementing TH is to create a standardized process to recognize NE in a timely manner. In this regard, it may be useful to develop a checklist based on neurological criteria derived from the Sarnat or Thompson encephalopathy scores [5,6]. Additionally, a video teaching tool would be helpful in order to better standardize neurological evaluations. Training should explain the inclusion and exclusion criteria, the hypothermia procedure and the rewarming process. As soon as resuscitation is complete and eligibility for TH is confirmed, cooling should be started and continued until the infant is transferred.

The implementation of TH should include a targeted list of better practices including the following: ensure timely identification of infants with NE; develop a coordinated system with the local or regional referral cooling center; develop a transport team capable of performing passive and/or active cooling during transport and to continuously monitor core temperature (rectal or esophageal). At the referral-cooling center, a protocol should be developed for providing and monitoring TH, including early detection of cooling side-effects, and implemented through continual staff education. A standard protocol for electroencephalograph/amplitude-integrated electroencephalograph (EEG/aEEG) monitoring in conjunction with local neurophysiologists can be set up. It may not be very easy to recognize NE early and to select infants that could benefit from TH. The combination of aEEG and neurologic examination shortly after birth enhances the ability to identify high-risk infants and increases the positive predictive value and specificity compared with either method alone [7]. Broader utilization of aEEG, which is simple to implement and interpret, should make it easier to obtain objective and earlier assessments of the neurologic prognosis.

A protocol for obtaining magnetic resonance imaging (T1, T2 and diffusion images) in the first 10 days of life must be established. Within a regional network, healthcare workers should be trained to assess the outcomes of TH by using standard neurodevelopmental scales. All pediatricians and midwifes within the regional perinatal network should have formal basic and, if possible, advanced simulation trainings. An information packet with descriptions of the register and training material should be provided.

2.2. Inclusion criteria

The goal of any TH program should be the early identification of infants with the highest risk for encephalopathy. The severity of encephalopathy should be determined using a list of specific inclusion criteria, which requires a neurological examination. A standardized neonatal neurologic examination should be used before starting TH and repeated at set intervals. Sarnat stage or Thompson score could be used to guide the decision to cool infants. A Thompson score $\geq$7 and moderate–severe Sarnat encephalopathy grade at 3–5 h after birth both predict an abnormal 6 h aEEG [8].

The inclusion criteria for TH should be devised based upon the recently published scientific evidence from several large, randomized clinical trials (RCTs) [9–11] and should be approved by a national consensus. Infants with suspected HIE who meet the following criteria should be considered for treatment with cooling: infants with >36 completed weeks of gestation who are aged <6 h with at least one of the following: (i) an Apgar score of $\leq$5 at 10 min after birth; (ii) continuous need for resuscitation, including endotracheal or mask ventilation, at 10 min after birth; (iii) acidosis, defined as a pH <7.00 and a base deficit $\geq$16 mmol/L in umbilical cord or any blood sample (arterial, venous or capillary) within 60 min of birth. It should then be determined whether these infants meet the neurological abnormality entry criteria. For neurological abnormalities, infants must fulfill one or both of the following criteria: (i) moderate-to-severe encephalopathy; or (ii) seizures. If an infant meets these criteria, but cooling is not offered, the reasons behind this decision as well as dialogue with the regional NICU should be clearly documented in the medical notes. If an infant does not meet the criteria for cooling but the local clinicians believe cooling may be beneficial, the regional NICU should be contacted for further advice.

The aEEG is one of the best predictors of neurological outcome following HIE. Abnormal aEEG within 6 h of birth was used to assign infants into trials of neuroprotection with hypothermia. aEEG detects electrical seizures and provides information on regional background cerebral activity. However, recent data have shown that for neonates with HIE the predictive value of the aEEG recorded within 6 h of birth for adverse outcome at 18 months of age was reduced in infants treated with cooling compared with infants who were not cooled [12,13]. Although clinicians were advised to perform EEG or aEEG recording whenever possible during the first three days of life, aEEG monitoring prior to TH was not a mandatory requirement according to the French guidelines. These changes from the published RCT were approved at the national level to avoid delaying the initiation of hypothermia treatment when EEG or aEEG were not available. Useful prognostic information can be obtained from EEGs performed within 24 h and repeated at 48 h of admission with an additional EEG at one week of age [14].

2.3. When to start cooling

Cooling should be started as soon as possible after resuscitation is completed and eligibility is confirmed. Current evidence suggests that cooling is maximally beneficial when it is commenced within 6 h of birth. The interval to initiation of hypothermia in newborn infants is based on experimental data. Results of these studies indicated a therapeutic window of ~6 h following an ischemic event; delay in induction of hypothermia beyond 8 h was associated with attenuation or loss of neuroprotection [15,16]. Other recent animal studies suggested a deleterious effect from cooling when delayed by 12 h in case of severe hypoxia–ischemia [17].

French guidelines recommended starting TH as soon as possible within the first 6 h of life with a target temperature range of $33 \pm 0.5^{\circ}$C but a rectal temperature $\leq 36^{\circ}$C during the initial phase of stabilization and transport.

2.4. Where should infants with hypothermia be treated?

When an infant has been identified as suitable for cooling, the local or regional cooling center should be contacted. Centers that introduce treatment with TH should designate a lead contact person and harbor the following criteria: (i) have facilities for providing full intensive care; (ii) have the capability to perform neonatal brain MRI before discharge, ideally between 5 and 10 days after birth; (iii) have expertise in obtaining and interpreting aEEG and/or continuous EEG; (iv) utilize a multidisciplinary approach in the long-term follow-up of the infants. Theoretically, all neonatal intensive care units (NICUs) are eligible for TH.

The French recommendations suggested that TH should only be carried out in units that have experience in the care of severely ill neonates and by staff who have been specifically trained in the use of TH. In France, this recommendation has been interpreted as applying to the large-network NICUs. Neonatal units in France are organized into three categories: local neonatal unit (level I), special