Foundations in Newborn Care

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Hypoxic Ischemic Encephalopathy and Hypothermic Intervention for Neonates

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ABSTRACT

Perinatal asphyxia and resulting hypoxic ischemic encephalopathy (HIE) occur in 1 to 3 per 1000 births in the United States. Induced hypothermia as an intervention for asphyxiated infants offers promising results in reducing neurodevelopmental disabilities in surviving infants. Induced hypothermia and selective head cooling are effective interventions for asphyxiated infants that minimize continued neuronal damage and decrease neurodevelopmental disability at 18 months of age. Identification of affected infants immediately after delivery and transfer to a facility that provides this therapy is necessary to maximize the potential of this intervention. Standardization of hypothermia protocols within neonatal intensive care units is essential for providing hypothermia as a treatment of HIE in infants. This article explores the pathophysiology of HIE, identifying infants at risk for HIE as a result of perinatal asphyxia, the use of hypothermic intervention for compromised infants, and barriers to the implementation of treatment.

KEY WORDS: HIE, hypothermia, hypoxic ischemic encephalopathy, neonates, perinatal asphyxia, selective head cooling, total body cooling

Perinatal asphyxia and resulting hypoxic ischemic encephalopathy (HIE) occur in 1 to 3 per 1000 births in the United States.[1-3] Higher rates occur in developing countries with limited diagnostic and interventional resources.[1] Worldwide, 10% to 60% of infants who develop HIE will die and at least 25% of the survivors will have long-term neurodevelopmental sequelae.[2] Hypoxic ischemic encephalopathy is the primary cause of 15% to 28% of cerebral palsy among children.[3] Hypothermic therapy as either selective head cooling (SHC) or total body cooling as an intervention for asphyxiated infants offers promising results since its experimental inception in the late 1990s. This article examines the pathophysiology of HIE, identifies infants at risk for HIE as a result of perinatal asphyxia, reviews hypothermic intervention as a primary intervention for compromised infants, and describes barriers to its implementation.

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SEARCH STRATEGY

A key word search was conducted using PubMed and the Cochrane Collection databases. Search terms included hypoxic ischemic encephalopathy, HIE, hypothermia, neonates, and total body and SHC. Specific search limits included infants only, English only, and articles published within the last 7 years. Search results yielded 2 large, randomized, controlled trials with more than 200 patients in each trial that explored hypothermia in neonates. Seven articles explored neurodevelopmental outcomes, distribution of cerebral lesions, and determinants of outcomes. Smaller randomized controlled trials exploring hypothermia for neonates were also included. Other articles explored the pathophysiology of HIE and side effects of hypothermia interventions in neonates.

PATHOPHYSIOLOGY OF PERINATAL ASPHYXIA AND THE DEVELOPMENT OF HIE

Acute hypoxic brain injury in a neonate can occur for a variety of reasons. Any condition that leads to decreased oxygen supply (hypoxia) and decreased blood supply to the brain (ischemia) can lead to this condition. Acute perinatal events such as placental abruption, umbilical cord prolapsed,

uterine rupture, tight nuchal cord, or an acute blood loss are risk factors.[3]

In response to hypoxia, the neonate's brain converts to anaerobic metabolism in an effort to sustain functional ability. Anaerobic metabolism leads to rapid depletion of adenosine triphosphate, accumulation of lactic acid, and failure of normal metabolic activity.[4] Intracellular pumps lose their efficiency resulting in an accumulation of sodium, calcium, and water within brain cells. The resulting cascade of events includes an accumulation of fatty acids, increasing oxygen-free radicals, cell apoptosis, and cell death.[4] Following the acute injury and resuscitation, the neonate's brain will experience a second delayed insult if there is no intervention, despite restoration of oxygen to the brain.

Once cerebral perfusion and oxygenation are restored, a second cascade of injury will occur at 6 to 48 hours because the brain attempts to restore function.[4] Phosphorus metabolites and intracellular pH are restored; however, the brain has not recovered from the initial injury and mitochondrial dysfunction continues. The neonate's body releases endogenous inflammatory cells and mediators following the initial injury that contribute to ongoing brain injury in the second phase.[4] The second stage of brain cell injury is characterized by restoration of cellular metabolism with continued suppression of electroencephalogram activity.[5] Cell apoptosis and death occur following hypoxic injury, and the extent of cell death is proportional to the extent of the ischemic injury.

Perinatal asphyxia progresses to HIE based on the degree of brain injury and resulting clinical presentation. Clinical seizures are the hallmark of resulting encephalopathy following injury.[1,4] Sarnat and Sarnat's criteria for clinical encephalopathy can be used to determine the degree of neuronal injury based on the infant's symptoms.[6] The Sarnat and Sarnats criteria include lethargy, stupor, or coma, with 1 or more of hypotonia, abnormal reflexes (oculomotor or papillary abnormalities), an absent or weak suck, or evidence of seizures.[6] An amplitude-integrated electroencephalogram (aEEG) can provide further information about the degree of brain injury. Moderate to severe voltage changes seen on an aEEG are indicative of encephalopathy and further intervention is required to limit brain injury.[1]

Perinatal asphyxia and resulting HIE cannot be anticipated prior to delivery. Neuronal injury is a result of precipitous events, rather than a diagnosis or known complication of the pregnancy. Asphyxiated and physiologically depressed infants show no clinical warning of delivery complications that can be anticipated during the pregnancy. During labor, variable and late decelerations of the fetal heart rate are the main indicators of a stressed infant at risk for hypoxic injury.[4] Primarily, term infants are at risk for neuronal injury because of change in blood flow and brain metabolic activity after 34 weeks.

There is no known genetic predisposition for developing HIE for some infants compared with other infants. There is also no evidence exploring individual coping and adaptation processes among infants that can blunt neuronal injury following asphyxia.

THERAPEUTIC HYPOTHERMIA

Mild hypothermia as a treatment for HIE was discovered in the 1950s when isolated reports that asphyxiated infants were submersed in a cold tub of water until spontaneous respirations began.[7] In the 1980s, it was noted that hypothermic drowning victims survived submersion for up to 40 minutes with no lasting neurologic sequelae and experiments with hypothermia were conducted following cardiopulmonary resuscitation of adults.[7] Studies have also explored the use of hypothermia with stroke and cardiac patients.

Today, the effects of hypothermia on the neonatal brain following acute brain injury are well known and promising. A temperature reduction by 2°C to 4°C decreases the rate of cell death and delays the cascade of metabolic changes that are normally associated with hypoxia.[4] As a result, cerebral metabolism is reduced, adenosine triphosphate stores are conserved, anaerobic metabolism effects are blunted, and free radicals are not released. In addition, hypothermia can delay secondary brain injury and mitigate present injury in the neonatal hypoxic brain.[4]

CoolCap Trial

Mild hypothermia for asphyxiated infants emerged in the late 1990s as a possible intervention for brain injury occurring between the initial phase and the second phase of neuronal damage associated with HIE. The first randomized controlled trial and cornerstone of hypothermic intervention in neonates was the CoolCap trial.[6] This trial recruited 234 infants with evidence of asphyxia and resulting encephalopathy from 25 perinatal centers between July 1999 and January 2002 to participate in the trial. Strict inclusion criteria in the CoolCap trial has allowed benchmarking with further criteria in later HIE studies. Inclusion criteria of the CoolCap trial included the following[6]:

1. gestational age 36 weeks or more,
2. Apgar score of 5 or less at 10 minutes following birth,
3. continued need for resuscitation (endotracheal or mask ventilation) at 10 minutes following birth,
4. severe acidosis (pH $<$ 7.00, base deficit $\geq$ 16 mmol/L from umbilical cord, or an arterial or venous sample from infant within 1 hour following birth), and

5. grade II or III encephalopathy based on the Sarnat and Sarnat criteria.

The CoolCap trial cooled infants ($n = 116$) to 34°C to 35°C rectally via a cooling cap within 6 hours of delivery and maintained a hypothermic state for 72 hours. The control infants ($n = 118$) received conventional care and maintained temperatures of 36.5°C to 37.2°C.

The results demonstrated that infants cooled prior to 6 hours following delivery had the most potential to benefit from the therapy before the second phase of neuronal damage occurred.[6] The infants had aEEGs performed prior to the initiation of therapy. Infants in the cooling group with the most severe aEEG changes received less benefit from cooling than infants with less severe aEEG changes. The study found that the initial encephalopathy grading was more predictive of future adverse outcomes than the Apgar scores or the presenting acidosis.[6] The authors recommended aEEG recordings to identify at-risk infants who could benefit from hypothermia before the small therapeutic window of 2 to 6 hours following delivery closed.

The CoolCap trial also concluded that larger infants responded better to hypothermia than smaller infants. The authors speculated that the size of the brain could affect the temperature to which it was cooled in relation to outcomes, but more research was needed.[1,6] Pyrexia (temperature > 38°C) was clearly associated with worse outcomes, especially in the control group, since heat production increased cerebral metabolism and exacerbated neuronal injury.[1] Inadvertent warming occurred in both the cooling and control groups through seizures, inflammatory cytokine release, and the use of servo-controlled heaters.

Complications of Hypothermia in Neonates

The safety of induced hypothermia and SHC has been studied in relation to the risk–benefit ratio of the treatment in neonates. Hemodynamic changes associated with hypothermia remain the major negative outcome of the intervention. One study[8] analyzed the hemodynamic parameters of 7 cooled infants by comparing cooling values with postrewarming values. The most significant side effect of cooling was a decrease in heart rate, with a mean of 129 beats per minute compared with a mean of 149 beats per minute following rewarming. Cardiac output was reduced to 67% and stroke volume was reduced to 77% while the infants were cooled, but all infants returned to baseline following rewarming.[8] None of the infants experienced an alteration in blood pressure or left ventricular ejection time as a result of hypothermia. The authors concluded that despite a decrease in heart rate, stroke volume, and cardiac output, the infants were able to maintain peripheral perfusion with normal lactate levels during the hypothermia phase with all the parameters returning to baseline with passive rewarming.[8] The authors also cited heart arrhythmias, hypotension with rapid rewarming, and increased blood viscosity as potential side effects of hypothermia, but no infant in their study experienced these side effects.

A second study looked at 26 asphyxiated infants with hypothermia as an intervention for half of the infants.[9] All of the cooled infants had some degree of renal impairment that resolved with rewarming. All of the cooled infants demonstrated a fall in heart rate, less than 80 beats per minute in 2 infants, which resolved with rewarming. One cooled infant had a prolonged QT interval that resolved following rewarming. None of the cooled infants required an increase in oxygen requirement compared with the control infants. The authors found that coagulopathies within the cooling group were not significant when compared with the control group. There was no difference in the rates of thrombocytopenia, intraventricular hemorrhage, or abnormal coagulation tests in the cooled group when compared with the control group.[9] An additional study[3] found no association with an increase in hemorrhagic lesions in infants cooled to 33°C to 34°C when examining basal ganglia and white matter lesions in asphyxiated infants.

Studies examining the side effects of hypothermia acknowledge transient hemodynamic changes in cooled infants who resolve with passive rewarming.[3,8,9] All studies recommend hypothermia for asphyxiated infants as the benefits of preventing continued neuronal damage outweighed the transient hemodynamic side effects. The original CoolCap trial data did not specifically address side effects, but the same data were used in other trials focusing on side effects and the safety of hypothermia.

Neurodevelopmental Outcomes Following Hypothermia in Neonates

Using the original data obtained from the CoolCap trial, investigators were able to follow up with the infants who participated in the study to evaluate neurodevelopmental outcomes at 18 months of age.[6] Of the original 234 infants who participated in the CoolCap trial, 218 infants were available for follow-up at 18 months. Investigators defined *severe neurodevelopmental disability* as a triad of symptoms, including gross motor function of 3 to 5 (nonambulant, sits with support, or infants with no self-mobility), Bayley mental development index less than 70, and bilateral cortical visual impairment served as the threshold indicators for severe neurodevelopmental disability.[6] The authors found that 73 of the 110 infants in the control group (66%) experienced death

or severe disability by 18 months compared with 59 of 108 infants in the cooled group (55%). It was also noted that for infants with the most severe changes in aEEG recordings prior to treatment, hypothermia had offered minimal neuroprotective benefit and that some infants incurred too much brain damage from the initial injury to benefit from any interventional treatment.[6]

Rutherford et al[3] explored cerebral lesions found in HIE infants who underwent cooling compared with normothermic infants. Cooling in this particular study was divided into infants who had SHC and infants who had whole body cooling (WBC). Cerebral lesions related to asphyxia and HIE are most commonly found in the basal ganglia and thalamus and are associated with the development of cerebral palsy.[3] Less commonly, lesions are found in the white matter of the brain and are associated with later cognitive impairments.[3] Eighty-six infants were enrolled in the study by Rutherford et al to determine whether cooling altered the severity and pattern of lesions found in infants with HIE. Thirty-four cooled infants (20 were whole body cooled and 14 were selective head cooled) and 52 normothermic infants were evaluated following recovery from an acute hypoxic injury. The study found that the prevalence of intraventricular hemorrhage was the same for all 3 groups but that the 2 cooling groups had a decrease in number and severity of basal ganglia and thalamic lesions.[3] In the control group, 46 of the 52 infants (88%) had basal ganglia and thalamic lesions present. Seven of 14 infants (50%) in the SHC group and 15 of 20 infants (75%) in the WBC group had basal ganglia and thalamic lesions present. Approximately 40% of infants with significant basal ganglia and thalamus lesions will have white matter infarction but in this study there was no decrease in the incidence of severe white matter lesions in the cooled infants.[3]

Shankaran et al[10] conducted a large hypothermia trial with 208 enrolled infants with similar inclusion criteria to that of the CoolCap trial. The researchers recruited infants from 15 perinatal centers from July 2000 to May 2003. Two hundred five infants received follow-up neurodevelopmental assessments at 18 to 22 months. Death or moderate or severe disability occurred in 44% of the infants in the cooling group (n = 102) and in 62% of the infants in the control group (n = 103). Table 1 illustrates the infants stratified based on disability from Shankaran's results.

TABLE 1. Outcomes at 18 to 22 months of age[10]

	Cooled Infants (n = 102)	Controlled Infants (n = 103)
No. of deaths	24	38
Cerebral palsy, %	19	30
Blindness, %	7	14
Hearing aid use, %	4	6

Cooling and Rewarming

Since the CoolCap Trial, researchers have explored various methods of cooling and the degree of cooling required to mitigate neuronal injury resulting from HIE. The original CoolCap was a cooling device shaped as a hat that circulated water to maintain the infant's rectal temperature at 34°C to 35°C. Selective head cooling seemed ideal because the infant's brain produces 70% of total body heat and systemic side effects of hypothermia would be minimal with only the infant's head cooled.[2] However, new research indicates that WBC enables the infant to reach a deeper level of hypothermia, and deep internal brain structures benefit from temperatures of 33°C.[3,10] Shankaran et al[10] chose WBC for their randomized control trial since WBC provides even cooling to all brain structures affected by hypoxic injury. Because the thalamus, internal capsule, and basal ganglia of the brain are most sensitive to hypoxic injury, WBC achieved homogenous hypothermia compared with SHC, which tends to cool the periphery of the brain rather than the central brain. The hemodynamic side effects of hypothermia do not differ between SHC and WBC.[8] Stratified studies have divided cooled infants into SHC and WBC and into differing degrees of cooling that complicate the results and delay translation into practice.[3,9] Cooling temperatures ranged from 33°C to 35° via rectal, skin, and esophageal measurements in the studies, with no standardization evident.[1,2,5,6,10]

Once the infant has been in a hypothermic state for 48 to 72 hours, the process of rewarming begins. As with the cooling of infants, the process of rewarming infants varied among trials. In 1 study, active rewarming occurred over 3 to 6 hours with the discontinuation of the cooling device and the addition of blankets and a radiant warmer.[8] Wyatt et al[1] and Shankaran et al[10] rewarmed infants slowly, no faster than 0.5°C per hour until temperature was normothermic.

However, one point on temperature is clear. Temperatures greater than 38°C following acute neuronal injury increased cerebral metabolism and intensified injury. The CoolCap trial cautioned against inadvertent warming of infants in both the control and cooled groups through seizure activity and the use of servo-controlled warmers.[1]

Limitations and Gaps in the Literature

The current literature on mild hypothermia is variable in translation and future application. The CoolCap

trial was the first multicenter, randomized controlled trial to evaluate hypothermia as an effective intervention following perinatal asphyxia. Subsequent studies have used the original inclusion criteria and incorporated recommendations from the CoolCap trial so now neonates must be enrolled within 6 hours of delivery to qualify for a hypothermia study and an aEEG is most often the diagnostic tool used to determine baseline neuronal abnormality.

The neurodevelopmental outcomes of hypothermia are promising but have not been validated by repeated studies. The studies that examined neurodevelopmental outcomes all measure different outcome criteria and continue to demonstrate high rates of disability despite treatment. Despite discouraging rates of disability, hypothermia still has benefits if initiated promptly and uniformly. Healthcare providers should acknowledge that the severity of the initial hypoxic injury is most prognostic of the infant's outcomes, regardless of intervention. Another limitation of neurodevelopmental outcomes is time. Because hypothermia is relatively new, there are no data on how these infants will progress as they age and how they will perform in cognitive exercises.

In summary, what is known about hypothermia as an intervention for neonates with traumatic brain injury is that it is safe and affords minimal hemodynamic side effects. Hypothermia should be initiated as soon as possible because the therapeutic window closes 6 hours after initial injury at delivery. Hypothermia has decreased the degree of neurodevelopmental disability for some infants, but infants with more severe neuronal injury may not respond to any intervention.

What is not known about hypothermia for neonates is the ideal cooling temperatures, method of cooling, or duration of cooling because data have varied across studies. The duration of therapy in the studies ranged from 48 to 72 hours and it was often discontinued early for perceived hemodynamic instability of a decreased heart rate related to hypothermia. Unfortunately, rewarming practices of cooled infants vary as much as the initial cooling practices.

Neurodevelopmental outcomes are premature because of the short amount of time that the intervention has been available. It is apparent that more research is required despite encouraging outcomes to date.

Implications for Nursing Practice

Access to hypothermia for infants with acute asphyxia at delivery varies across the United States. An anonymous survey about hypothermia and HIE was sent to the 809 medical directors of neonatal intensive care units in the United States in October 2005. Only 28 of the 441 respondents (6.4%) offered cooling as an intervention for HIE at their institution.[11] Of the respondents who cooled infants, 64% offered total body cooling and 25% offered head cooling, the remainder a combination of both interventions. Lang et al[11] reported that the majority of institutions that offered cooling were academic centers, with an average patient census greater than 40. Approximately half (57%) of the centers offered Extra Corporeal Membrane Oxygenation. Overwhelmingly, 69.1% of the responders felt that they "need more data" to determine whether hypothermia was an effective intervention for infants with HIE.[11] A major limitation of this survey was the convenience sample model, but it offers a glimpse into the access issue for infants born in community hospitals with acute asphyxia and a narrow therapeutic window for successful intervention with hypothermia.

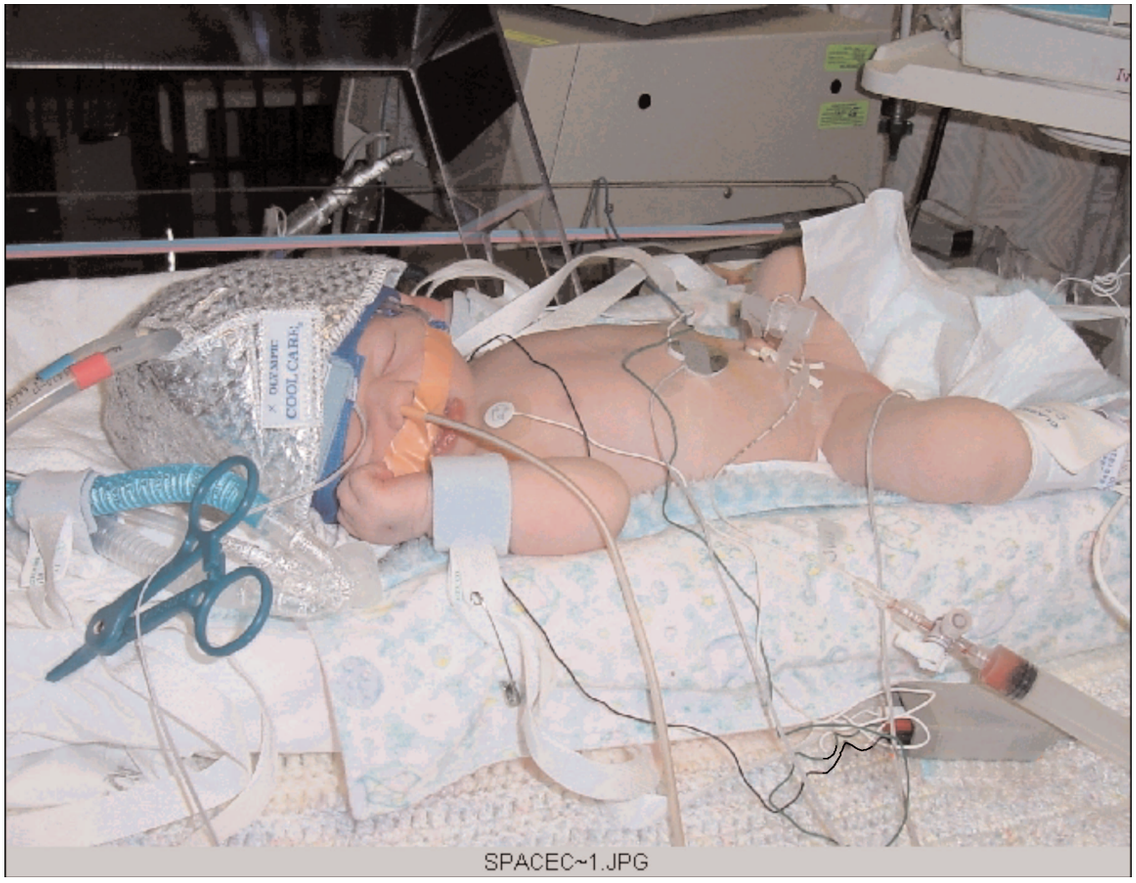
Nursing is central to the identification of infants at risk for developing HIE as a result of acute asphyxia at delivery. After the initial hypoxic injury, infants may appear to recover, but this leads to a false sense of safety because a second phase of neuronal injury will inevitably follow. Ideally, infants at risk for HIE should be transferred to a treatment center within 6 hours to prevent further brain injury and to initiate hypothermia. Education about the clinical presentation of asphyxia, presence of seizures, and criteria for hypothermia should be mandatory for all labor and delivery, newborn nursery, and neonatal intensive care unit nurses, regardless of whether hypothermia is practiced at that institution or not.

Although it is essential to initiate hypothermia for at-risk infants as soon as possible, it is equally imperative that it is initiated in a controlled manner and in a setting with hypothermia expertise. The transferring hospital should not begin hypothermic procedures independently prior to transfer. Efforts to avoid overheating the infant should be made. If the patient cannot be transferred within 6 hours of delivery, cooling can be initiated in transport, but only under the direction of the accepting institution.[12] Whole body cooling is easier to initiate than SHC in transport with ice packs and the use of ambient air temperature while continuously monitoring rectal temperatures.

Care of the infant receiving either SHC or total body cooling requires a whole systems approach (Figure 1). In addition to managing the cooling apparatus, supportive care of the infant is essential. Promotion of oxygen and ventilation is important. Not all infants who qualify for hypothermic therapy will require mechanical ventilation. However, careful attention should be paid to avoid hypoxia, hyperoxia, or hypercarbia.[13,14]

Cooling will frequently result in a mild decrease in resting heart rate. However, bradycardia (a heart rate less than 80 beats per minute) may indicate that the infant needs to be warmed slightly. In addition, perfusion should be maintained and hypotension should be treated with volume expansion or vasopressor drugs as appropriate. Monitoring of intake and output is essential because infants with asphyxia injury may

FIGURE 1.



Infant with cooling cap in place. Used with permission from Dr Jan Paisely.

also develop oliguria secondary to acute tubular necrosis or "syndrome of inappropriate antidiuretic hormone" release.[14]

Total parental nutrition will be required to maintain appropriate blood glucose and provide for nutrition. Hypoglycemia and hyperglycemia should be avoided.[14] In addition, electrolytes, including sodium and potassium, should be monitored, along with coagulopathy studies.

It is generally preferable that infants receiving cooling therapy be sedated as necessary. Excess activity or agitation can result in elevation of body temperature. Infants with HIE are at risk for seizure activity. Seizures should be identified and treated.[13]

Advanced practice nurses are pivotal in the application of research into practice. They can increase what is known about therapeutic hypothermia for neonates through formalized teaching arenas, publication, and informal unit-based in-services with nursing staff. Education should focus on identifying at-risk infants who require intervention, describing the benefits of hypothermia, and gaps in the literature regarding hypothermia in neonates. In turn, nurses can educate families and caregivers about this intervention for their infant and support them emotionally as their infant's prognosis evolves. Advanced practice nurses should participate in further research to contribute to the knowledge of hypothermia for neonates. Standardization of hypothermia practice is the goal as more is discovered about this life-saving intervention.

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