Induced hypothermia to treat neonatal hypoxic-ischemic encephalopathy

Review of literature with meta-analysis and development of national protocol

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ABSTRACT

قمنا بتقييم فعالية تطبيق البرودة لتدبير اعتلال الدماغ الاقفاري بنقص الأكسجة عند حديثي الولادة مكتملي الحمل في 6 دراسات بحثية. أظهرت التحليلات التلوية لهذه الدراسات أن تطبيق المعالجة بالتبريد خلال الست ساعات الأولى من الولادة عند المصابين باعتلال الدماغ الاقفاري بنقص الأكسجة متوسط إلى شديد الدرجة قلل من نسبة الوفاة والأختلاطات العصبية عند عمر العام والنصف، الخطورة النسبية = 0.81 (95% فاصل الثقة من 0.71 إلى 0.93)، القيمة المعيارية=0.002 الخطورة المتغايرة = 0.11 (95% فاصل الثقة من 0.18 إلى 0.4–) مع رقم يحتاج إلى معالجة=9 (95% فاصل الثقة من 5 إلى 25). بالإضافة لذلك بينت تلك الأبحاث أن المعالجة بالتبريد قد ترافقت مع زيادة في نسبة البقاء سليماً، الخطورة النسبية = 1.53 (95% فاصل الثقة من 1.22 إلى 1.93) القيمة المعيارية <0.001، الخطورة المتغايرة = 0.12 (95% فاصل الثقة من 0.06 إلى 0.18) مع رقم يحتاج إلى معالجة=8 (95% فاصل الثقة من 5 إلى 17). لقد طورنا برتوكولاً وطنياً مستخدمين طرق ميسرة من التبريد. سيؤدي هذا البروتوكول إلى انتشار تطبيق المعالجة بالتبريد في مختلف المراكز في بلدنا.

The efficacy of induced hypothermia to treat hypoxic-ischemic encephalopathy (HIE) in term infants has been evaluated in 6 multicenter randomized controlled trials. Meta-analysis of these trials shows that hypothermia in the first 6 hours after moderately severe HIE reduced the risk rate of death or neurological impairment at 18 months of age; risk ratio (RR): 0.81 (95% confidence interval [CI]: 0.71 to 0.93, p=0.002); risk difference -0.11 (95% CI: -0.18 to -0.04), with a number needed to treat of 9 (95% CI: 5-25). It also showed that treatment with hypothermia was associated with an increased rate of intact survival; RR: 1.53 (95% CI: 1.22-1.93, p<0.001); risk difference: 0.12 (95% CI: 0.06-0.18), with a number need to treat of 8 (95% CI: 5-17). We developed a national protocol using a simplified method of cooling. This protocol will hopefully lead to a widespread implementation of induced hypothermia in different settings within Saudi Arabia.

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Hypoxic-ischemic encephalopathy (HIE) continues to be a major cause of death or poor long-term neurodevelopmental outcome.[1-4] Until recently, there were no therapies other than supportive measures for perinatal HIE. Although Westin reported the use of hypothermia for "asphyxia neonatorum" in 1955,[5] it is only in the past decade that systematic studies have been carried out to address the safety and efficacy of this therapy in HIE. The efficacy and safety of moderate hypothermia to treat newborns with HIE were examined in several pilot studies with promising results.[6-15] Six large randomized controlled trials showed a reduction in the mortality rate and improved neurodevelopmental outcome when induced hypothermia was used to treat moderate HIE.[16-21]

Although there is a great interest in hypothermia as a potential neuroprotective strategy for perinatal HIE, yet to date, there are no published guidelines for its utilization. Therefore, a thorough review of the literature was conducted in addition to an updated meta-analysis of the available data to establish a well-defined national protocol for the use of induced hypothermia in HIE.

Our attempt aimed to develop a uniform approach for the use of induced hypothermia in HIE in Saudi Arabia as a step to improve the outcome of these infants.

Pathogenesis of hypoxic-ischemic encephalopathy. Brain injury after hypoxic-ischemic (HI) insult is an evolving process. It starts with initial injury (primary phase) due to hypoxia-ischemia with primary brain oxidative metabolism impairment. The nature and severity of the primary phase dictates the severity and extent of the initial damage. This primary phase is followed by a reperfusion period during which the brain oxidative metabolism recovers partially or completely (latent phase or window of opportunity) to be followed by another phase of secondary deterioration (secondary phase) during which brain cells continue to die for longer periods.[22] The severity of this delayed energy failure is correlated with adverse neurodevelopmental outcome at one and 4 years of age.[2]

The processes of cell injury and death during the primary phase are easy to understand and appear to include: deprivation of oxygen and nutrients with a secondary anaerobic glycolysis, depletion of high-energy phosphate reserves, accumulation of lactic acid, calcium, free radicals and excitatory neurotransmitters such as glutamate in the extracellular space, and loss of cell membrane functions. If the injury process is not reversed, it will lead to acute cell death (primary cell death). However, after the reperfusion starts the biochemical processes involved in cell death are more complex, including intracellular influx of calcium, injury from inflammatory mediators and free radicals, and mitochondrial dysfunction. These processes trigger apoptotic cell death (secondary cell death), which may evolve over hours, days, or weeks. The main 2 factors that might affect the length of this phase include the severity of the initial injury and the maturational stage of the brain.[23]

Animal studies and small clinical trials. Gun et al[24] showed in fetal sheep that brain cooling to around 32° and 34°C started 5.5 hours after cerebral ischemia and before post ischemic seizures was neuroprotective, and diminished the extent of parasagittal neuronal loss. Animal studies also concluded that brain cooling should be initiated as early as possible after brain injury, preferably within 2 hours, but not later than 6 hours (therapeutic window); the rectal temperature should be reduced in the range of 32-34°C for effective brain cooling; and cooling should be continued for around 72 hours. In a newborn animal model, optimal methods for rewarming were not tested, but, adult animal studies showed that slow rewarming was better.[22-29] However, the experimental animal HI model differs from the human "perinatal encephalopathy" in its causation, timing, nature severity, and the underlying status of the human brain, such as its maturity, nutritional and hormonal status, inflammatory, and preexisting developmental abnormalities. All these factors are known to alter brain response to acute insults.

Gunn et al,[6] in 1998 reported the first randomized controlled study, which demonstrated that selective head cooling is feasible and safe in term infants with moderate-to-severe HIE. Azzopardi et al[8] reported the use of amplitude integrated electroencephalography (aEEG) to select newborn infants with poor neurodevelopmental outcome after HIE, and instituted moderate whole body hypothermia. They concluded that newborn infants can be early selected by aEEG, and induced moderate whole body hypothermia was feasible and safe. Thoresen and Whitelaw[9] showed that mild therapeutic hypothermia could be accomplished without serious short-term cardiovascular adverse effects. The findings from these studies concluded that induced hypothermia in newborn infants with HIE is feasible and safe without serious acute complications. In a randomized controlled multicenter pilot study of whole body hypothermia, in infants with severe HIE, Eicher et al[12] were the first to report long-term outcome with a better rate of survival and neurodevelopment at 12 months of age in the hypothermia group compared with the control group. Shankaran et al[10] also confirmed the feasibility of whole body hypothermia using the servo controlled cooling system (Blanketrol 11 Hyper-Hypothermia system, Model 222R, Cincinnati Sub-Zero Products, Inc., Cincinnati, OH, USA) with the esophageal temperature at 34.5°C without major short-term complications.

Large clinical trials. Selective head cooling. In the first international multicenter trial (CoolCap),[16] 234 infants with acute perinatal HIE were enrolled. Inclusion criteria were as follows: >36 weeks gestation; an Apgar score of 5 or less at 10 minutes after birth; a continued need for resuscitation, including endotracheal or mask ventilation at 10 minutes after birth; or severe acidosis, defined as pH <7.0 or a base deficit of 16 mmol/L or more in an umbilical cord blood sample or an arterial or venous blood sample obtained within 60 minutes of birth; and a modified Sarnat score and aEEG criteria consistent with a diagnosis of moderate-to-severe HIE. One hundred and sixteen infants in the experimental group received selective head cooling with mild systemic hypothermia induced with a cooling cap device (Olympic Medical Cool Care System, Olympic Medical, Seattle, WA, USA) in which cold water was circulated. The rectal temperature was maintained

between 34-35°C for 72 hours, and the infants were re-warmed at a rate <0.5°C per hour. Conventional intensive care with normal body temperature was provided for 118 infants in the control group. Ninety-three percent of enrolled infants were available for follow-up at 18 months. Primary outcome, defined as death or severe disability at 18 months of age, was met in 55% of the cooled infants, and in 66% of the control subjects. A logistic regression analysis controlling for baseline aEEG severity, presence of seizures, and age at randomization indicated a possible benefit from hypothermia, odds ratio (OR) 0.57 (95% confidence interval [CI]: 0.32-1.01, p=0.05). In a predetermined subgroup analysis of HIE severity (based on pre-randomization aEEG changes), the investigators found that although no evidence of benefit was observed in those with the most severe changes in the pre-randomization aEEG (n=46), a significantly improved outcome was seen in the less severe cases (n=172), OR 0.42 (95% CI: 0.22-0.80, p=0.009). A significant protective effect from hypothermia was observed when baseline clinical severity was added to the regression model, OR 0.52 (95% CI: 0.28-0.70, p=0.04).

The China cooling study[20] randomly assigned full term infants with HIE to selective head cooling or control group. The cooling was initiated within 6 hours after birth for a nasopharyngeal temperature of 34±0.2°C and rectal temperature of 34.5-35.0°C in the intervention group. Neurodevelopmental outcome was evaluated at 18 months of age. The primary outcome was a combined end point of death and severe disability. One hundred and ninety-four infants were analyzed (100 infants in the selective head cooling group and 94 infants in the control group). The combined outcome of death and severe disability was 31% in the selective head cooling group, and 49% in the control group, OR 0.47 (95% CI: 0.26-0.84, p=0.01), the mortality rate was 20% in the selective head cooling group, and 29% in the control group, OR 0.62 (95% CI: 0.32-1.20, p=0.16), and the severe disability rate was 14% in the selective head cooling group, and 28% in the control group, OR 0.40 (95% CI: 0.17-0.92, p=0.01).

Whole body hypothermia. The first large randomized controlled whole body hypothermia trial, enrolled 208 infants from 16 Neonatal Research Network centers (NICHD), and studied the effect of whole body hypothermia in moderate-to-severe HIE.[17] Eligibility criteria included gestational age ≥36 weeks, a pH of ≤7.0 or a base deficit of ≥16 mmol/L. If pH were between 7.01 and 7.15, a base deficit was between 10 and 15.9 mmol/L, or if blood gases were not available, additional criteria including an acute perinatal event and either a 10-minute Apgar score of 5 or less or assisted ventilation initiated at birth and continued for at least 10 minutes, were required. Infants were candidates when seizures or moderate or severe encephalopathy was present. Infants randomized to whole body hypothermia (n=102) were placed on a cooling blanket (Blanketrol II Hyper-Hypothermia System, Cincinnati Sub-Zero, Cincinnati, OH, USA) to keep esophageal temperature at 33.5±0.5°C for 72 hours followed by slow rewarming, while the control infants (n=106) were given standard intensive care. The primary outcome; death or moderate/severe disability occurred in 44% of the hypothermia group, and 62% of the control group, risk ratio (RR): 0.72 (95% CI: 0.54-0.95, p=0.01), with a number needed to treat (NNT) of 6. The mortality rate was 24% in the hypothermia group and 37% in the control group, the RR was 0.68 (95% CI: 0.43-1.01, p=0.08). Other outcomes included disabling cerebral palsy, which occurred in 19.2% of the hypothermia group versus 30% of the control group, RR: 0.68 (95% CI; 0.38-1.22), blindness, which occurred in 7% of the hypothermia group versus 14% of the control group, RR: 0.50 (95% CI: 0.17-1.44) and hearing impairment requiring a hearing aid was 4% in the hypothermia group, and 6% in the control group, RR: 0.54 (95% CI: 0.10-3.02).

The Total Body Cooling Trial (TOBY)[18] was an international randomized controlled trial, comparing intensive care plus total body cooling for 72 hours with intensive care without cooling. Eligibility criteria included gestational age ≥36 weeks, 10 minutes Apgar score of ≤5, or a continued need for resuscitation at 10 minutes of life and within 60 minutes after birth, acidosis (defined as any occurrence of umbilical cord, arterial, or capillary pH of <7.0 or base deficit of 16 mmol per liter). In addition, they had to have a clinical diagnosis of moderate-to-severe encephalopathy and have abnormal background activity of at least 30 minutes duration, or seizures on aEEG. Hypothermia was achieved by a cooling blanket (Tecotherm TS 200, Tec-Com, Munich, Germany) and the target rectal temperature was set between 33-34°C. The primary outcome at 18 months of age was a composite of death or severe neurodevelopmental disability in survivors. In the cooled group (163), 42 infants died and 32 survived with severe neurodevelopmental disability, whereas in the noncooled group (162), 44 infants died and 42 had severe disability, RR for either outcome, 0.86 (95% CI: 0.68-1.07, p=0.17). The rate of survival without a neurologic abnormality was significantly increased in the cooled group, 44% versus 28% in the noncooled group, RR: 1.57 (95% CI: 1.16-2.12, p=0.003).

In the neo.nEURO.network randomized controlled trial,[19] term neonates with HIE were assigned randomly to either a control group or a hypothermia group at a rectal temperature of 33.5°C (range: 33-34°C) with a cooling blanket (Tecotherm TS 200, Tec-Com, Munich, Germany) for 72 hours. All infants in both groups received morphine (0.1 mg/kg) every 4 hours or an equivalent dose of fentanyl. The primary outcome, at the age of 18-21 months, was death or severe disability. A total of 111 infants were evaluated at 18-21 months (53 in the hypothermia group, and 58 in the normothermia group). The primary outcome was observed in 51% of the hypothermia group and 83% of the normothermia group, OR: 0.21 (95% CI: 0.09-0.54, p=0.001), NNT 4 (95% CI: 3-9). In the severe HIE group, hypothermia also had a statistically significant protective effect (n=77), OR: 0.17 (95% CI: 0.05-0.57, p=0.005). There were also fewer clinical seizures in the hypothermia group.

The ICE (Infant Cooling Evaluation) study[21] was a randomized controlled trial, which was recently completed aiming to determine the effectiveness and safety of whole body cooling in term newborns with HIE using clinical eligibility criteria and a simple method of hypothermia initiated at the birth hospital. This prospective multicenter international randomized controlled trial enrolled newborns of 35 weeks' gestation or more, with moderate-to-severe clinical encephalopathy and indicators of peripartum hypoxia-ischemia within 6 hours of birth. Hypothermia was passively induced by turning off the radiant warmer, with refrigerated gel packs applied as required to maintain rectal temperature at 33-34°C for 72 hours; 'control' infants rectal temperature was maintained at 36.8-37.3°C. One hundred and ten in the cool group, and 111 in the control group were randomized from 28 participating centers. Therapeutic hypothermia reduced the primary outcome, risk of death or major sensorineural disability at 2 years of age, 51.4% in cool infants versus 66.3% in control infants; RR: 0.77 (95% CI: 0.62-0.98, p=0.03). Survival, free of any disability, was also increased.

Meta-analysis of large, multicenter, clinical randomized control trials. We compiled a dataset of 1311 infants from 6 large randomized controlled trials for whom neurological outcomes up to at least 18 months of age were available.[16-21] A summary of the trials characteristics is provided in **Table 1**. These 6 trials: the trial by the CoolCap study group,[16] a National Institute of Child Health and Human Development (NICHD) study,[17] TOBY trial,[18] ICE trial,[21] neo.nEURO.network trial,[19] and the China Cool Cap trial[20] had similar entry criteria. The infants were ≥36 weeks' gestation who had evidence of birth asphyxia, and moderate or severe encephalopathy. The CoolCap[16] and TOBY[18] trials also included abnormal aEEG as an inclusion criterion. In all trials, random allocation was completed by 6 hours after birth.

The primary outcome for all 6 trials was the combined rate of mortality and disability. Disability was defined in the CoolCap,[16] TOBY,[18] and neo.nEURO.network,[19] and China Cool Cap[20] trials as the presence of at least one of the following impairments: mental development index score of less than 70 on the Bayley scales of infant development; gross motor function classification system level of ≥3 out of 5; or bilateral cortical visual impairment with no useful vision. The NICHD trial[17] defined disability as a mental developmental index score of 70-84 and one or more of the following: gross motor function classification system level ≥2; hearing impairment with no amplification; or a persistent seizure disorder. Whereas, major sensorineural disability in the ICE trial[21] comprised neuromotor delay; cerebral palsy (CP) in which the child was not walking (moderate CP) or was unlikely to walk (severe CP) at 2 years, a Psychomotor Development Index score on the Bayley

Table 1 - Summary of randomized trials included in the meta-analysis.

Study	Mode of cooling	Cooled: control	Primary outcome	Follow-up
CoolCap trial (Gluckman et al)[16]	Selective	116:118	Death and severe disability	18 months
China trial (Zhou et al)[20]	Selective	100:94	Death and severe disability	18 months
NICHD trial (Shankaran et al)[17]	Whole body	102:106	Death, moderate, and severe disability	18 months
TOBY trial (Azzopardi et al)[18]	Whole body	163:162	Death and severe disability	18 months
neo.nEURO trial (Simbruner et al)[19]	Whole body	64:65	Death and severe disability	18 months
ICE trial (Jacobs et al)[21]	Whole body	110:111	Death and severe disability	24 months

CoolCap - CoolCap Study Group,[16] China - China Study Group,[20] NICHD - National Institute of Child Health and Human Development,[17] TOBY - Total Body Hypothermia,[18] neo.nEURO - neo.nEURO.network,[19] ICE - Infant Cooling Evaluation[21]

Scales of Infant Development II [BSID-II] of less than -2 SDs, blindness (vision worse than 20/200 in both eyes), and/or deafness requiring amplification.

Each of these 6 trials showed a reduction in the risk of mortality and disability in infants who underwent therapeutic hypothermia. Meta-analysis of these trials showed that therapeutic hypothermia significantly reduced the risk of death or disability at 18 months (**Figure 1**); RR: 0.81 (95% CI: 0.71-0.93, p=0.002); risk difference -0.11 (95% CI: -0.18 to -0.04) with NNT of 9 (95% CI: 5-25). Hypothermia also had significantly lowered the rates of severe disability (p=0.006), cerebral palsy (p=0.004), severe neuromotor delay (psychomotor developmental index score <70, p=0.02), severe neurodevelopmental delay (mental developmental index score <70, p=0.01), and blindness (p=0.03). Furthermore, 4 trials, which reported rate of intact survival, showed that treatment with hypothermia was associated with an increased rate of intact survival (**Figure 2**); RR: 1.53 (95% CI: 1.22-1.93, p<0.001); risk difference 0.12 (95% CI: 0.06-0.18) with an NNT of 8 (95% CI: 5-17).

Suggested national protocol. We developed a national protocol for induced hypothermia to treat HIE in full term neonate (**Appendix 1**). The aim of this protocol is to help in the widespread use of hypothermia and to unify the method of cooling in Saudi Arabia. The inclusion and exclusion criteria used were similar to those of the TOBY trial.[18] The suggested method of cooling is simple, practical, and was previously tested.[21,30]

Discussion. In the absence of any specific treatment to improve the poor outcome of infants with HIE, clinical interest for induced hypothermia as a new treatment is understandable. The meta-analysis of the above-mentioned 6 large trials provides strong evidence that moderate hypothermia is efficacious and safe in infants with HIE. The trials included in this review used a similar inclusion criteria and primary outcome. The hypothermia effect on primary outcome showed a notable consistency in all the trials, which should give confidence in the therapeutic benefit of moderate hypothermia. However, later neurodevelopmental follow-up, particularly at school age, must be carried out to detect any cognitive or behavioral problems

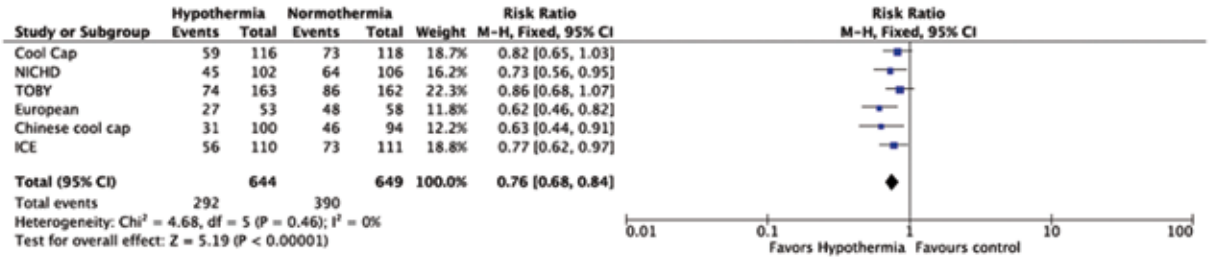

Figure 1 - Primary outcome; death and neuro-developmental disability at 18 months. Forest plot of the effect of therapeutic hypothermia compared with standard care (normothermia) on primary outcome; death or disability ("events"). All infants randomly assigned to either study arm were included in the analysis. A Mantel-Haenszel fixed effects model was used to calculate risk ratios and 95% confidence intervals (CI). Test for heterogeneity: X^2=0.82, degrees of freedom=2 (p=0.66); I2=0%. Test for overall effect: Z=3.03 (p=0.002). Studies shown are CoolCap - CoolCap Study Group,[16] NICHD - National Institute of Child Health and Human Development,[17] TOBY - Total Body Hypothermia,[18] neo. neuro - neo.nEURO.network,[19] China - China Study Group,[20] ICE - Infant Cooling Evaluation.[21]

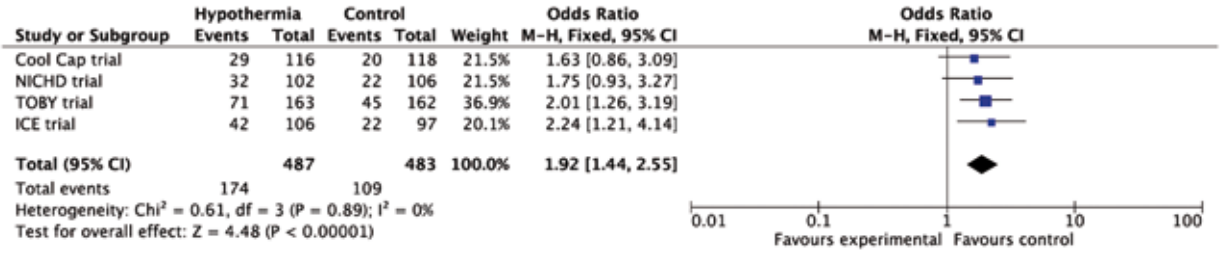

Figure 2 - Survival with normal neurological function. Forest plot of the effect of therapeutic hypothermia compared with standard care (normothermia) on survival with normal neurological function ("events"). All infants randomly assigned to either study arm were included in the analysis. A Mantel-Haenszel fixed effects model was used to calculate risk ratios and 95% confidence intervals (CI). Test for heterogeneity: X^2=0.05, degrees of freedom=2 (p=0.66); I2=0%. Test for overall effect: Z=3.66 (p=0.0003). Studies shown are CoolCap - CoolCap Study Group,[16] NICHD - National Institute of Child Health and Human Development trial,[17] TOBY - Total Body Hypothermia trial,[18] ICE - Infant Cooling Evaluation trial.[21]

and confirm long-term neurological benefits of this intervention.

The optimal mode of cooling (whole body or selective head) is unknown, especially with regard to their differential protective effects, if any, on various regions of the brain (generalized cortical versus deep brain nuclei). The trial design features and the entry criteria for the TOBY trial,[18] whole body, were intentionally made similar to those of the CoolCap trial,[16] selective head. Thus, the findings from the 2 trials can be effectively compared to assess the relative benefits from whole body versus selective head cooling in HIE. The primary and the secondary outcomes of the 2 trials were similar. However, further research is needed to definitely sort out this matter.

In the 6 trials reviewed, findings are particularly remarkable given the differences between the studies in the way cooling was induced. As well, within the whole body cooling trials, the NICHD,[17] the TOBY,[18] the neo. nEURO network,[19] and the ICE,[21] the hypothermia was achieved by different cooling methods. The TOBY[18] and ICE trials,[21] but not the CoolCap,[16] NICHD,[17] neo.nEURO network trials,[19] or china study,[20] cooled infants during transport to the treatment center, but the age at start of cooling was similar in the 6 trials. The minimal effect of these differences on the primary outcome increases confidence that any reliable cooling method that can be generalized to a wider healthcare system is satisfactory, and that clinicians planning the widespread implementation of therapeutic hypothermia need be less concerned about the precise method of cooling and more focused on training of staff for its safe application.

The suggested national protocol (**Appendix 1**) was developed using most acceptable inclusion and exclusion criteria. A simplified method of cooling is used in this protocol, which we tested for the last 10 years and found easy and reliable.[30] This protocol will hopefully lead to a widespread implementation of induced hypothermia in different settings within Saudi Arabia. Data collected from the use of such a unified protocol will help to assess neurodevelopmental outcome of treated infants in the future.

Perinatal HIE is not a single disease from a single cause, with great diversity in the timing and magnitude of brain injury. It is unreasonable to expect that any single intervention will provide uniformly favorable outcome. Therefore, other interventions may help to potentiate the effect of hypothermia. Simbruner et al[19] suggested that co-treatment with an opioid with its neuroprotective proprieties may positively influence the hypothermia effect in their population. Recent studies showed that administration of systemic recombinant erythropoietin (rEPO) could reduce the risk of death or disability for term infants with moderate HIE, but not for those with severe HIE.[31-33] Ongoing trials of Xenon may prove to be helpful adjunctive therapy in HIE.[34,35]

In conclusion, the present data strongly support the use of therapeutic hypothermia in newborn infants with HIE to reduce the risk of death and neurological impairment. Continued follow-up of the children enrolled in these studies is essential to determine whether these benefits are maintained in later childhood. Based on the available evidence, at the current time, therapeutic hypothermia should be considered as standard therapy for full term newborn infants with moderate-to-severe HIE. The suggested national protocol, using a simplified method of cooling, will hopefully encourage widespread use of hypothermia in our country.

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Appendix 1 - National protocol for whole body hypothermia to treat hypoxic-ischemic encephalopathy (simplified method).

Inclusion criteria:

Assessment to be carried out as soon as possible; within the first 2 hours of life. Infant must meet both physiologic and neurologic criteria.

1. **Physiologic criteria:** Evidence of intrapartum hypoxia, including either of:
   - A. Cord (or baby's arterial blood gas [ABG] carried out within the first one hour of life), pH <7.0 and base deficit (BD) of ≥16 mmol/L.
   - B. Cord (or baby's ABG carried out within the first one hour of life), pH 7.0-7.15 and BD of 10-15.9 mmol/L with an acute perinatal event (for example, abruption placenta, cord prolapse, significant fetal heart rate abnormalities like variable or late decelerations) + 1 or 2.
     1. Apgar score ≤5 at 10 minutes.
     2. Mechanical ventilation or resuscitation at 10 minutes.

2. **Neurologic criteria:** any one of the followings.
   - A. The presence of seizures (seizures due to hypoxic-ischemic encephalopathy (HIE) is an automatic inclusion criterion).
   - B. Physical exam consistent with moderate-to-severe encephalopathy (Thompson score >7).[36]
   - C. Abnormal (discontinuous, continuous low voltage or burst suppression and absent awake/sleep cycling) amplitude integrated EEG (if available).

Exclusion criteria:

1. Gestational age <35 weeks or birth weight <2000 gr.
2. Major congenital malformation.
3. Unable to initiate cooling within 6 hours of age (at discretion of the consultant).
4. Life threatening coagulopathy.
5. The need for fractionated inspired oxygen ≥0.9 (to reconsider again as soon as oxygenation improves).

Cooling procedure:

1. Prepare the bed using overhead warmer (incubator could be used instead):
   - A. Do not turn on overhead warmer.
   - B. Place the cooling bags (first aid cold/hot gel pack), kept in fridge at 5-6°C.
   - C. Place a thin bed sheet over the cooling bags to avoid direct contact with the infant.

2. Place the infant on top of cooling bags, making sure that cooling bags are on full contact with infant's body. Reposition the infant every 6 hours and assess skin.

3. Document time when cooling was initiated (hour 0). Cooling will continue for 72 hours.

4. Monitor core temperature continuously using a rectal probe, inserted to 4-5 cm, desired core temperature is 33-34°C. Skin temperature should be monitored as secondary reading. All decisions regarding the cooling should be carried out using the rectal temperature.

5. Monitor continuously infant's heart rate (HR), respiratory rate, blood pressure, temperature and pre and post saturation. The vital signs should be record every one hour during the cooling period. Tolerate HR as low as 70 bpm as long as it is sinus rhythm and blood pressure and saturation are normal.

6. Maintain the core temperature between 33-34°C by adding, changing, or removing cooling bags.

7. Nurse to patient ratio should be 1:1 during the cooling and rewarming periods.

What to expect during cooling:

1. Decrease in heart rate and mild increase in blood pressure.

2. Increase in urine output.

3. Mild changes in glucose level.

When to interrupt the cooling process:

1. Decrease cooling to core temperature of 35-35.5°C when FiO2 ≥0.7.

2. Stop cooling when FiO2 ≥0.9, or when significantly abnormal coagulation studies.

Investigations:

1. At start of cooling:
   *complete blood count (CBC), renal function (BUN, Cr, Na, k, Ca), coagulation studies (PT, APTT, INR), liver function test (LFT), blood gases.

2. During cooling and rewarming:
   * Renal function, blood gases daily, and as needed.
   * CBC daily.
   * Glucose every 6 hours.

3. Magnetic resonance imaging will be carried out at 7-10 days of life (if available).

Nutrition and sedation:

1. Keep nil per mouth during the cooling and rewarming period (occasionally may feed if stable).

2. May use sedation if the patient is irritable or in pain.

Rewarming:

1. Start rewarming after completion of 72 hours of whole body cooling.
2. Gradually increase the infant's core temperature by 0.5°C per hour to 36.5°C (goal temperature).
3. Do the rewarming by gradually removing the cooling bags one at a time.
4. If all bags are removed and infant's core temperature continues to be less than 36°C, the overhead warmer can be switched on to help maintaining the infant's temperature.
5. Record core and skin temperatures every 30 minutes and other vital signs (HR, blood pressure, saturation) every 2 hours.
6. Once goal temperature is achieved, record temperature every 2 hours and other vital signs every 4 hours.

What to expect during rewarming:

1. Increase in heart rate and mild decrease in blood pressure.

2. Decrease in urine output.