Abstract

**Background:** The Induced Hypothermia (IH) and Optimizing Cooling (OC). trials for HIE had similar inclusion criteria. The rate of death/moderate-severe disability differed for the subgroups treated with TH at 33.5°C for 72 hours (44% vs. 29%, unadjusted p=0.03). We aimed to evaluate differences in patient characteristics and care practices between the trials.

**Methods:** We compared pre/post-randomization characteristics and care practices between IH and OC.

**Results:** There were 208 patients in the IH trial, 102 cooled, and 364 in the OC trial, 95 cooled to 33.5°C for 72 hours. In OC, neonates were less ill, fewer had severe HIE, and the majority were cooled prior to randomization. Differences between IH and OC were observed in the adjusted difference in the lowest PCO2 (+3.08mmHG, p=0.005) and highest PO2 (−82.7 mmHG, p<0.001). In OC compared to IH the adjusted RR of exposure to anticonvulsant prior to randomization was decreased (RR 0.58, (0.40-0.85), p=0.005) and there was increased risk of exposure during cooling to sedatives/analgesia (RR1.86 (1.21-2.86), p=0.005).

**Conclusion:** Despite similar inclusion criteria, there were differences in patient characteristics and care practices between trials. Change in care practices over time should be considered when planning future neuroprotective trials.
Introduction

Therapeutic hypothermia (TH) has been widely adopted into clinical practice for treatment of moderate to severe neonatal encephalopathy secondary to presumed perinatal asphyxia. The five large randomized trials of TH demonstrated a significant reduction in the risk of death and disability compared to non-treated neonates; however, there remain a large proportion of neonates who die or develop disability despite treatment. (1) Following animal studies that suggested further benefit of deeper TH or longer duration of treatment, the NICHD Neonatal Research Network (NRN) performed the Optimizing Cooling (OC) trial. The OC trial randomized newborns with moderate or severe encephalopathy to 4 hypothermia regimens: 33.5°C for 72 hours (usual treatment), 33.5°C for 120 hours; 32°C for 72 hours; and 32°C for 120 hours. However, this trial was stopped early for safety and futility and later animal studies question the potential benefit and possible harm of deeper or longer cooling. (2, 3) A lower death rate was observed in the usual treatment arm compared to the longer and/or deeper cooling arms. When comparing outcomes from the OC trial to the initial NRN Induced Hypothermia trial (IH), patients in the usual care arm of OC had lower unadjusted rates of in-hospital death and death or neurodevelopmental disability (7% vs. 19%, p=0.02) and (29% vs. 44%, p=0.03), respectively. (4, 5) Enrollment criteria and study procedures in the OC trial were similar to the original IH trial except that clinical cooling could be initiated prior to randomization Neonates were excluded if they had a temperature recorded of < 32°C for 2 hours.

It is important to understand possible reasons for the lower rate of death or disability in the "standard of care" arm of the OC trial as other trials of adjunctive treatment to hypothermia are currently on-going or in development. Changes in clinical care may contribute to the observed differences in morbidity and mortality rates. Secondary analyses TH trials reported on the associations between blood gas tensions of carbon dioxide(6), oxygen(7), and blood glucose levels(8) and outcome. The use of sedation and analgesia may have also changed between trials however its association with outcome is controversial(9, 10). Changes in the approach to the identification, diagnosis and treatment of seizures have been cited in the literature with potential impact on outcome. (11–14) Intensive care by a team now experienced in the provision of TH may have differentially impacted the clinical outcome of patients in the OC trial. Finally, as the OC trial was initiated, TH was recognized as a safe and effective treatment likely resulting in increased focus on the recognition and enrollment of eligible patients, particularly those with moderate encephalopathy, and shorter time to initiation of TH. However, therapeutic drift is also occurring with treatment being applied to neonates who may not have met all of the criteria outlined by the trials. Registry data in the UK confirm an increase in the use of TH after the TOBY trial with concern for therapeutic drift between 2007-2011 indicating that patients with less severe Hypoxic Ischemic Eencephalopathy (HIE) are now being treated. (15) Further systematic analysis of patient characteristics and clinical care practices among infants enrolled in the two trials of TH may provide helpful information for planning future trials and determining sample size. Our objective was to perform an analysis of differences in patient characteristics and care practices between the IH and OC trials.
Methods

Enrollment into the IH and OC trials occurred 2000-2003 and 2010-2013, respectively, at NICHD NRN centers (15 centers in IH and 18 centers in OC). The institutional review board at each NRN center approved the trial protocols. Inclusion criteria for both trials were similar and as follows: neonates born at a gestational age of at least 36 weeks and admitted to an NRN center within 6 hours of birth, the presence of physiologic criteria, and seizures (clinical or electrographic) or moderate to severe encephalopathy identified by a certified examiner using a standardized modified Sarnat examination.(4,16,17) A training session for research personnel was held to standardize the neurologic examination and each site principal investigator certified additional neonatologists to perform the neurologic examinations. Encephalopathy was defined as the presence of moderate or severe signs in 3 out of the following 6 categories: level of consciousness, spontaneous activity, posture, tone, primitive reflexes, and autonomic nervous system. The number of moderate or severe signs determined the severity of encephalopathy at enrollment and if the number of signs were equally distributed then the determination was based on level of consciousness. There were definitional differences in the OC trial in the categories of tone and one sub-category of neonatal reflexes, suck. In the OC trial, both hypotonia and hypertonia were defined as moderate abnormalities where in IH only hypotonia was included. In the severe category for tone, a neonate could be described as flaccid or rigid while in IH only flaccid was used. For moderate abnormalities in suck reflex the presence of a ‘bite’ was added to the description of a ‘weak’ suck used in IH. Exclusion criteria for both trials were similar except for the addition of a core temperature of less than 32.5°C for at least 2 hours prior to randomization for the OC trial. Passive or active cooling was allowed prior to randomization in the OC trial.

For all neonates enrolled in the IH trial (N=208) and all enrolled in the OC trial (N=364) we compared maternal and baseline neonatal characteristics, and variables reflecting resuscitative measures at birth. To evaluate subtle differences in the severity of encephalopathy between the two trials, we compared the distribution of the severity of findings in the pre-randomization modified Sarnat exam categories in neonates determined to have moderate HIE and those with severe HIE between the two trials. In the subgroup of IH infants (n=102) randomized to therapeutic hypothermia (33.5°C for 72 hours) and OC infants (n=95) randomized to usual cooling (33.5°C for 72 hours) we also compared baseline maternal and neonatal characteristics.

Specific clinical care practices prior to and during the 72 hours of treatment were compared between the two groups treated with cooling at 33.5°C for 72 hours in IH and in OC. The following variables were analyzed: lowest PCO2 and highest PO2 levels; lowest and highest blood glucose levels; proportion of neonates who were intubated and mechanically ventilated, Fraction of inspired oxygen (FiO2), use of anticonvulsant medication, analgesics and sedatives, inotropic agents prior to baseline, at baseline (defined as time esophageal probe was placed and initiation of study treatment), and at 24, 48 and 72 hours of treatment. Differences in the use of EEG and short-term outcomes including, electrographic seizures, length-of-stay, need for gastrostomy tube or gavage feeds at discharge, discharge on anticonvulsant medications and in-hospital death were evaluated. The primary outcome of each trial, death or moderate or severe disability at 18–22 months was compared.
definition of moderate or severe disability was similar in both trials.\(^4,5\) To assess cognitive
development, in the IH trial the Bayley II was used and in OC the Bayley III, developed in
2006, was used. The cutoffs for moderate or severe cognitive impairments were identical in
both studies, each reflecting either one or two standard deviations (± 15) below the
population mean of 100 respectively. A mental developmental index (MDI) on the Bayley II
or a cognitive score in the Bayley III of 70-84 was used as part of the definition for moderate
and an MDI or cognitive score of < 70 was used as part of the definition of severe disability.

**Statistical Analyses**

Chi-square tests (or Fisher’s exact test) for categorical variables, and t-tests for continuous
variables were used to evaluate differences in maternal and neonatal baseline characteristics,
care practices, and outcome measures. Logistic and linear regression analysis were used to
evaluate differences in care practices and outcome between the subgroups in IH treated with
TH and those in the usual care arm of OC with adjustment for severity of HIE and center (as
a random effect) to evaluate differences in the primary outcome of death or disability
between the IH and OC trials. Tests for interaction between severity of encephalopathy and
trial (IH or OC) were performed.

**Results**

**Maternal and Neonatal Characteristics**

Maternal and baseline neonatal characteristics of all subjects enrolled in the IH and OC trials
as well as those randomized to the cooling arm of the IH trial (33.5°C for 72 hours) and the
usual care arm of the OC trial (33.5°C for 72 hours) are shown in Table 1. In the OC trial,
maternal thyroid disease, hypertension, and hemorrhage were more common than in the IH
trial while uterine rupture occurred more frequently in IH than OC. Fewer neonates in OC
were delivered by emergent cesarean section. Compared to OC, neonates enrolled in IH had
more frequent: Apgar score of less than 5 at 10 minutes after birth, lower pH and greater
base deficits, intubation at delivery, delayed onset of spontaneous respirations, severe
encephalopathy, and clinical seizures prior to randomization. In contrast, neonates enrolled
in OC compared to IH were born at slightly younger gestational ages and more were outborn
and thus transferred to a NRN center.

**Use of Pre-Randomization Cooling, Initiation of Cooling, and Temperature at Baseline**

The majority of subjects (69%) in OC were either passively or actively cooled prior to
randomization. In the usual cooling arm in OC, 70 of 95 (74%) were cooled prior to
randomization. 52 were clinically cooled (placed on a cooling device), 17 were cooled
passively, and 1 was cooled with ice/gel packs. Despite randomization occurring at a later
age in OC compared to IH (5.1 ± 1.0 h vs. 4.3 ± 1.3 h), subjects clinically cooled prior to
randomization in OC had cooling initiated earlier (3.8 ± 1.3 h vs. 5.0 ± 1.2 h, \(p<0.0001\)).
Overall mean age at initiation of cooling occurred earlier in OC, 4.2 ± 1.4 h compared to 5.0
± 1.2 h in IH, \(p<0.0001\).

Continuous temperature data prior to randomization was not available and after baseline
core temperature was measured every 15 minutes for the first 4 hours of intervention. At the
time of randomization 54% of those in OC and only 4% of subjects in IH had a temperature within one degree of goal temperature (32.5°C-34.5°C), p-value<0.0001. The age at which a core temperature of < 34°C was first documented occurred earlier in OC 5.27 ± 1.66 h compared to IH 5.83 ± 1.23 h, p=0.008 (t-test). Those who were cooled prior to randomization in OC (n=70) had a temperature of 33.8°C ± 1.4°C at randomization. Overall, neonates in OC had significantly lower mean temperatures at baseline (initiation of study intervention) compared to IH (34.6°C ± 1.8°C vs. 36.9°C ± 1.0°C, p-value < 0.0001).

**Modified Sarnat Examination**

Infants were diagnosed with moderate/severe encephalopathy if they had >3 of the 6 categories that were moderately or severely abnormal. Differences in the distribution of the severity of the modified Sarnat exam components in neonates determined to have moderate HIE at randomization (IH vs. OC) and those determined to have severe HIE (IH vs. OC) at enrollment are shown in Supplemental Table S1. For neonates with moderate HIE, the distribution of severity of abnormalities in level of consciousness, spontaneous activity, tone, and autonomic nervous system differed between IH and OC. For neonates with severe HIE at randomization, the distribution of severity of findings in the different exam categories was similar except for the autonomic nervous system, with the difference being in the subcomponent of respiration.

**Care Practices During Therapeutic Hypothermia**

Blood gas tensions of oxygen and carbon dioxide in the first 72 hours after birth differed between IH and OC with lower PCO$_2$ and higher PO$_2$ values being observed in IH compared to OC (Table 2). These differences in PCO$_2$ and PO$_2$ remained significant after adjustment for severity of encephalopathy and for center. At baseline (start of intervention) 90% of neonates in IH were intubated and on mechanical ventilation compared to 78% of those in OC, adjusted Relative Risk (RR) 0.85, 95% CI 0.73-0.99, p-value 0.04. At 24, 48, and 72 hours fewer subjects were intubated and on mechanical ventilation in OC compared to IH but these differences were not statistically significant after adjusting for severity of encephalopathy and center. FiO2 at baseline and at 24, 48, and 72hrs is shown in Table 2. Neonates in OC received a lower FiO2 compared to IH at baseline, 24, and 48 hours (p-value 0.004-0.03). The use of inotropic support was lower at all time points in OC but not statistically significant after adjusting for severity of encephalopathy and center. The adjusted RR of anticonvulsant exposure prior to randomization was significantly decreased in OC compared to IH, but did not remain significant at ≥24 hours. Analgesics and sedating medications were more frequently used in OC compared to IH and was statistically significant after adjustment for severity of encephalopathy and center at 24, 48, and 72 hours of treatment. A table describing the types of sedative and analgesic medications used in both studies is available as supplementary material (Supplemental Table S2).

**In-hospital, Discharge, and 18-22 Month Outcomes**

The frequency of the diagnosis of clinical or electrographic seizures prior to hospital discharge was similar (62% in IH vs. 55% in OC). Electroencephalograms (EEGs) were not required but were performed in 68% of patients in IH and 76% of those in OC; this difference was not statistically significant. Data on EEG confirmation of seizures was not
available for IH. In OC usual care arm, 76 patients had an EEG performed and 24% had electrographic seizures identified. The use of anticonvulsants at discharge was decreased in OC but this difference was not statistically significant after adjusting for severity of HIE and center (Table 3). Length of stay and need for gavage tube or gastrostomy feeds at discharge were similar between the trials. A significant difference in in-hospital death was present between the hypothermia treated patients in IH and OC (19% vs. 7%, P=0.02) and in primary outcome at 18-22 months (44% vs. 29%, p= 0.03). After adjusting for severity of HIE and center, the relative risk of in-hospital death (RR 0.46, 95% CI 0.17 – 1.27, p= 0.13) and the primary outcome (RR 0.73, 95% CI 0.47 – 1.15, p= 0.17), in OC compared to IH was not statistically significant. In moderate and severe groups alone, the frequencies of in-hospital death and the primary outcome were lower in OC compared to IH (Table 3), but this difference was not statistically significant. On multivariate analysis there was no interaction between severity of HIE and trial. Rates of cerebral palsy and distribution of the gross motor function classification system (GMFCS) are also shown in table 3.

Discussion

Therapeutic hypothermia treatment has emerged rapidly as the standard of care for moderate or severe HIE following completion of the initial clinical trials. There was rapid diffusion of this therapy around the US and abroad.\(^{15}\) In 2005, as the IH trial was published, only 6.4% of NICU directors reported utilizing TH and 30% felt it was effective or very effective but by 2011 this increased to 50% using TH and 85% felt it was an effective or very effective treatment.\(^{18}\) This increase in the use of TH likely led to the development of expertise in the care of central nervous system (CNS) and non-CNS organ dysfunction observed in this patient population. Multiple publications during this period focused on optimizing the clinical management of these patients.\(^{19}\) In this analysis we documented that both patient characteristics and care practices of infants receiving TH changed in OC relative to IH.

There were differences identified in both maternal and neonatal characteristics that may reflect differences in severity of perinatal asphyxia and encephalopathy between the two trials. We did not have obstetric practice data to compare in the two trials but identified that neonates in OC were born at slightly younger gestational ages and fewer were delivered by emergent cesarean section. In the OC trial, neonates were less critically ill after birth with higher pH and lower base deficits and fewer had severe encephalopathy (23% in OC versus 32% in IH). This difference in the proportion of subjects with severe encephalopathy despite using similar inclusion criteria may reflect unmeasured changes in obstetric practice, acceptance of hypothermia as a safe treatment as well as improved awareness of its effectiveness in reducing the risk of death or disability for neonates with moderate or severe encephalopathy.\(^{1}\) Evaluation of the distribution of the severity of modified Sarnat exam components identified differences in several categories in those with moderate HIE between the trials. In contrast, in those with severe HIE the only difference observed between OC and IH was in the distribution of the respiratory subcomponent of the autonomic nervous system. Despite the differences in patient characteristics, there was not a statistically significant difference in the adjusted risk of death or disability in OC compared to IH (RR 0.73, 95% CI 0.47-1.15, p=0.17).
Our analysis indicates that there were several changes in care practices between the two trials. The relative contribution of each difference in practice is not able to be determined in this study. A potentially important difference was the use of passive or active cooling prior to randomization in OC. Centers were encouraged to not delay initiation of clinical cooling and the majority of neonates in OC were cooled passively or actively before randomization. More than half of the patients in OC had core temperatures that were within one degree of goal temperature at study baseline. Pre-clinical and an observational study indicates that earlier onset of cooling delays the onset of secondary energy failure and that the latent phase duration is inversely related to the severity of the insult.\(^{(20–22)}\) Meta-analyses have not been performed evaluating the impact of earlier cooling on outcome, however there has been an educational focus on improving identification of eligible patients and timely initiation of TH.\(^{(23)}\) Thoresen et al. retrospectively analyzed a cohort of infants with HIE in which cooling initiation at < 3 hours after birth was associated with an improved motor outcome.\(^{(20)}\) Reasons for the initiation of cooling at < 3 and > 3 hours are not provided. The TOBY trial demonstrated a trend \((p=0.08)\) towards better outcomes in newborns cooled within 4 hours of birth.\(^{(24)}\)

Blood gas tensions of oxygen and carbon dioxide differed between the IH and OC trials, even after adjusting for severity of encephalopathy. This suggests that practitioners were more aware of the deleterious effects of hypocarbia and hyperoxia and perhaps reflects changes in management to respiratory care in order to minimize exposure to low carbon dioxide and high oxygen tensions. This may also reflect that infants in OC were less sick and therefore less likely to have hypocarbia and hyperoxia. Free oxygen radicals are thought to mediate the adverse effects of hyperoxia while hypocarbia is known to decrease cerebral blood flow. Both have been found in a multivariate model to be associated with adverse outcomes including death, cerebral palsy and poor developmental outcome.\(^{(6,25)}\)

Differences in the use of medications commonly used during cooling including inotropes, anticonvulsants and sedatives/analgesics were documented. Some may be related to differences in severity of illness, although in some cases the difference persisted after adjusting for severity of HIE at enrollment and for center. Changes in the use of anticonvulsants may be related to changes in seizure identification and management practices between the two trials. Neonates with HIE are known to be at high risk for the development of seizures, with a documented frequency ranging from 30-60% in recent studies.\(^{(13,26–29)}\) The use of EEG was higher in the OC trial and this may reflect the impact of multiple publications highlighting the high incidence of electrographic seizures.\(^{(13,29)}\) In 2011 the American Clinical Neurophysiology Society recommended that 24 hours of continuous EEG monitoring should be implemented in neonates with HIE.\(^{(11)}\) During this same period, there was increased awareness that many seizures are subclinical and that the diagnosis of seizures based on clinical exam is difficult and is known to be inaccurate regardless of the level of experience of the clinician.\(^{(30)}\) Seizures also likely impact outcome with prolonged electrographic seizures being independently associated and a risk factor for poor outcome.\(^{(31–33)}\) We also identified that fewer infants were discharged home on anticonvulsants in the OC trial compared to the IH trial although this difference was not statistically significant. Exposure of the immature brain to anti-epileptic drugs is known in animal studies to increase apoptosis and may alter behavior and cognition.\(^{(34)}\) In a cohort
study of hospital exposure to phenobarbital and/or levetiracetam, increased cumulative phenobarbital and/or levetiracetam exposure were both associated with decreased cognitive and motor scores although the degree of brain injury on imaging was not controlled for and the study did not address the impact of ongoing outpatient treatment with these medications. (35) Given the limited sample size it is difficult to evaluate the impact that a change in the use of both in-hospital and post-discharge anticonvulsants could have had on the primary outcome.

Finally, we also identified a difference in the use of sedation and analgesia between the trials with increased use in OC compared to IH during TH. Increased use of sedation/analgesia may reflect increased surveillance by practitioners to address patient comfort. The NRN did not prescribe the use of sedation or analgesia to participating centers. Use of analgesia during hypothermia was identified in the Simbruner trial of TH as a possible mechanism for improved efficacy in his trial.(36) The mechanism of action is not well understood but may be related to a reduction in cold stress and shivering and therefore a decrease in metabolic rate.(9) In a secondary analysis of the IH trial exposure to sedation/analgesia was not associated with the primary outcome.(10)

The risk ratios of death alone and death or disability after adjustment for center and level of encephalopathy suggest that at least part of the difference in mortality and disability between trials is related to patient acuity. Randomized controlled trials would be needed to determine the impact of earlier initiation of treatment, sedation/analgesia, monitoring for seizures, and thresholds to treat seizures on outcomes. It is also important to consider that TH is being applied in clinical practice to neonates with less severe perinatal asphyxia and encephalopathy including some with mild HIE.(37–39) Design of future trials of neuroprotection will need to consider the impact of the severity of perinatal asphyxia, degree of encephalopathy after birth, and common care practices.

Limitations

Given the small number of patients included in this analysis and who experienced the primary outcome, we are not powered to perform a multivariate model to determine the impact of differing care practices between the trials. Data elements collected were not all identical between the two studies and some direct comparisons were difficult. We were not able to determine if there were differences in obstetric practice between the trials that may have contributed to the differences in severity of illness although neonates in OC were born at a slightly younger gestational age and fewer were delivered by emergent cesarean section. There was likely variation in practice across and within centers in blood pressure, seizure management, and use of analgesics and sedatives as standard management guidelines were not part of either study protocol. Use of two different standardized tests, the Bayley II in IH and Bayley III in OC may limit the ability to make direct comparisons in outcome between the trials. Direct comparison between Bayley II (MDI) and Bayley III (Cognitive) scores in both preterm and term HIE populations have been published.(40) In both these populations, Bayley III cognitive scores are thought to underestimate the degree of impairment when compared directly to the Bayley II. In the term HIE population, a Bayley III cognitive score of < 85 identified all but 1 patient who had a Bayley II MDI of < 70.(40) Thus the use of
Bayley III in the OC trial with a cut off of <85 for moderate-severe cognitive impairment should identify all neonates with severe impairments as determined by the Bayley II but may have underestimated the frequency of those with mild-moderate impairments. Finally any differences observed may be related to chance.

Conclusions

Despite similar inclusion criteria between the two NRN trials of TH there were significant differences in patient characteristics at enrollment. In OC compared to IH, newborns were less critically ill, fewer had severe HIE, they were cooled earlier, anticonvulsant use was lower, there was less hypocarbia and hyperoxia, and use of sedation or analgesia was more prevalent. These demographic and care practice differences may have contributed to the unadjusted differences in survival and disability rates in the usual care arm of the OC trial when compared to the cooled arm of the IH trial, although these differences were no longer significant after adjustment. Severity of perinatal asphyxia, degree of encephalopathy, and care practices need to be considered in the design of future trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References:

1. Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG. Cooling for newborns with hypoxic ischaemic encephalopathy. Cochrane database of systematic reviews 2013;1:CD003311.
2. Davidson JO, Wassink G, Yuill CA, Zhang FG, Bennet L, Gunn AJ. How long is too long for cerebral cooling after ischemia in fetal sheep? J Cereb Blood Flow Metab 2015;35:751–8. [PubMed: 25605291]
3. Alonso-Alconada D, Broad KD, Bainbridge A, et al. Brain cell death is reduced with cooling by 3.5 degrees C to 5 degrees C but increased with cooling by 8.5 degrees C in a piglet asphyxia model. Stroke 2015;46:275–8. [PubMed: 25424475]
4. Shankaran S, Laptook AR, Ehrenkranz RA, et al. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. The New England journal of medicine 2005;353:1574–84. [PubMed: 16221780]

5. Shankaran S, Laptook AR, Pappas A, et al. Effect of Depth and Duration of Cooling on Death or Disability at Age 18 Months Among Neonates With Hypoxic-Ischemic Encephalopathy: A Randomized Clinical Trial. JAMA 2017;318:57–67. [PubMed: 28672318]

6. Pappas A, Shankaran S, Laptook AR, et al. Hypocarbia and adverse outcome in neonatal hypoxic-ischemic encephalopathy. J Pediatr 2011;158:752–8 e1. [PubMed: 21146184]

7. Sabir H, Jary S, Tooley J, Liu X, Thoresen M. Increased inspired oxygen in the first hours of life is associated with adverse outcome in newborns treated for perinatal asphyxia with therapeutic hypothermia. J Pediatr 2012;161:409–16. [PubMed: 22521111]

8. Basu SK, Kaiser JR, Guffey D, et al. Hypoglycaemia and hyperglycaemia are associated with unfavourable outcome in infants with hypoxic ischaemic encephalopathy: a post hoc analysis of the CoolCap Study. Arch Dis Child Fetal Neonatal Ed 2016;101:F149–55. [PubMed: 26283669]

9. Wassink G, Lear CA, Gunn KC, Dean JM, Bennet L, Gunn AJ. Analgesics, sedatives, anticonvulsant drugs, and the cooled brain. Seminars in fetal & neonatal medicine 2015;20:109–14. [PubMed: 25457080]

10. Natarajan G, Shankaran S, Laptook AR, et al. Association between sedation-analgesia and neurodevelopment outcomes in neonatal hypoxic-ischemic encephalopathy. J Perinatol 2018;38:1060–7. [PubMed: 29795315]

11. Shellhaas RA, Chang T, Tsuchida T, et al. The American Clinical Neurophysiology Society’s Guideline on Continuous Electroencephalography Monitoring in Neonates. Journal of clinical neurophysiology : official publication of the American Electroencephalographic Society 2011;28:611–7. [PubMed: 22146359]

12. Bonifacio SL, Glass HC, Peloquin S, Ferriero DM. A new neurological focus in neonatal intensive care. Nature reviews Neurology 2011;7:485–94. [PubMed: 21808297]

13. Nash KB, Bonifacio SL, Glass HC, et al. Video-EEG monitoring in newborns with hypoxic-ischemic encephalopathy treated with hypothermia. Neurology 2011;76:556–62. [PubMed: 21300971]

14. Wietstock SO, Bonifacio SL, McCulloch CE, Kuzniewicz MW, Glass HC. Neonatal Neurocritical Care Service Is Associated With Decreased Administration of Seizure Medication. Journal of child neurology 2015;30:1135–41. [PubMed: 25380602]

15. Azzopardi D, Strohm B, Linsell L, et al. Implementation and conduct of therapeutic hypothermia for perinatal asphyxial encephalopathy in the UK--analysis of national data. PLoS One 2012;7:e38504. [PubMed: 22719897]

16. Shankaran S, Laptook AR, Pappas A, et al. Effect of depth and duration of cooling on deaths in the NICU among neonates with hypoxic ischamic encephalopathy: a randomized clinical trial. JAMA 2014;312:2629–39. [PubMed: 25536254]

17. Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress. A clinical and electroencephalographic study. Arch Neurol 1976;33:696–705. [PubMed: 987769]

18. Harris MN, Carey WA, Ellsworth MA, et al. Perceptions and practices of therapeutic hypothermia in American neonatal intensive care units. American journal of perinatology 2014;31:15–20. [PubMed: 23456901]

19. Thoresen M Supportive care during neuroprotective hypothermia in the term newborn: adverse effects and their prevention. Clin Perinatol 2008;35:749–63, vii. [PubMed: 19026338]

20. Thoresen M, Tooley J, Liu X, et al. Time Is Brain: Starting Therapeutic Hypothermia within Three Hours after Birth Improves Motor Outcome in Asphyxiated Newborns. Neonatology 2013;104:228–33. [PubMed: 24030160]

21. Gunn AJ, Bennet L, Gunning MI, Gluckman PD, Gunn TR. Cerebral hypothermia is not neuroprotective when started after postischemic seizures in fetal sheep. Pediatr Res 1999;46:274–80. [PubMed: 10473041]

22. Gunn AJ, Laptook AR, Robertson NJ, et al. Therapeutic hypothermia translates from ancient history in to practice. Pediatr Res 2017;81:202–9. [PubMed: 27673420]
23. Takenouchi T, Cuaycong M, Ross G, Engel M, Perlman JM. Chain of Brain Preservation--a concept to facilitate early identification and initiation of hypothermia to infants at high risk for brain injury. Resuscitation 2010;81:1637–41. [PubMed: 20810200]

24. Azzopardi DV, Strohm B, Edwards AD, et al. Moderate hypothermia to treat perinatal asphyxial encephalopathy. N Engl J Med 2009;361:1349–58. [PubMed: 19797281]

25. Klingner G, Beyene J, Shah P, Perlman M. Do hyperoxaemia and hypocapnia add to the risk of brain injury after intrapartum asphyxia? Arch Dis Child Fetal Neonatal Ed 2005;90:F49–52. [PubMed: 15613575]

26. Low E, Boylan GB, Mathieson SR, et al. Cooling and seizure burden in term neonates: an observational study. Archives of disease in childhood Fetal and neonatal edition 2012.

27. Srinivasakumar P, Zempel J, Wallendorf M, Lawrence R, Inder T, Mathur A. Therapeutic hypothermia in neonatal hypoxic ischemic encephalopathy: electrographic seizures and magnetic resonance imaging evidence of injury. The Journal of pediatrics 2013;163:465–70. [PubMed: 23452588]

28. Wusthoff CJ, Dlugos DJ, Gutierrez-Colina A, et al. Electrographic seizures during therapeutic hypothermia for neonatal hypoxic-ischemic encephalopathy. Journal of child neurology 2011;26:724–8. [PubMed: 21447810]

29. Shah DK, Wusthoff CJ, Clarke P, et al. Electrographic seizures are associated with brain injury in newborns undergoing therapeutic hypothermia. Archives of disease in childhood Fetal and neonatal edition 2014;99:F219–24. [PubMed: 24443407]

30. Malone A, Ryan CA, Fitzgerald A, Burgoyne L, Connolly S, Boylan GB. Interobserver agreement in neonatal seizure identification. Epilepsia 2009;50:2097–101. [PubMed: 19490044]

31. Glass HC, Nash KB, Bonifacio SL, et al. Seizures and magnetic resonance imaging-detected brain injury in newborns cooled for hypoxic-ischemic encephalopathy. J Pediatr 2011;159:731–3 e1. [PubMed: 21839470]

32. van Rooij LG, Toet MC, van Huffelen AC, et al. Effect of treatment of subclinical neonatal seizures detected with aEEG: randomized, controlled trial. Pediatrics 2010;125:e358–66. [PubMed: 20100767]

33. Kharoshankaya L, Stevenson NJ, Livingstone V, et al. Seizure burden and neurodevelopmental outcome in neonates with hypoxic-ischemic encephalopathy. Developmental medicine and child neurology 2016;58:1242–8. [PubMed: 27595841]

34. Bittigau P, Sifringer M, Genz K, et al. Antiepileptic drugs and apoptotic neurodegeneration in the developing brain. Proc Natl Acad Sci U S A 2002;99:15089–94. [PubMed: 12417760]

35. Maitre NL, Smolinsky C, Slaughter JC, Stark AR. Adverse neurodevelopmental outcomes after exposure to phenobarbital and levetiracetam for the treatment of neonatal seizures. J Perinatol 2013;33:841–6. [PubMed: 24051577]

36. Simbruner G, Mittal RA, Rohlimann F, Muche R. Systemic hypothermia after neonatal encephalopathy: outcomes of neo.nEURO.network RCT. Pediatrics 2010;126:e771–8. [PubMed: 20855387]

37. Oliveira V, Singhvi DP, Montaldo P, et al. Therapeutic hypothermia in mild neonatal encephalopathy: a national survey of practice in the UK. Arch Dis Child Fetal Neonatal Ed 2018;103:F388–F90. [PubMed: 28942433]

38. Massaro AN, Murthy K, Zaniletti I, et al. Short-term outcomes after perinatal hypoxic ischemic encephalopathy: a report from the Children’s Hospitals Neonatal Consortium HIE focus group. J Perinatol 2015;35:290–6. [PubMed: 25393081]

39. Walsh BH, Neil J, Morey J, et al. The Frequency and Severity of Magnetic Resonance Imaging Abnormalities in Infants with Mild Neonatal Encephalopathy. J Pediatr 2017;187:26–33 e1. [PubMed: 28479101]

40. Jary S, Whitelaw A, Walloe L, Thoresen M. Comparison of Bayley-2 and Bayley-3 scores at 18 months in term infants following neonatal encephalopathy and therapeutic hypothermia. Developmental medicine and child neurology 2013;55:1053–9. [PubMed: 23927586]
**Table 1.**

Maternal and neonatal characteristics across all randomized patients and subgroups of TH treated IH trial and OC usual cooling arm

|                          | IH Trial (all patients) | OC Trial (all patients) | P-value | IH Trial (33.5 × 72hrs) | OC Trial (33.5 × 72hrs) | P-value |
|--------------------------|-------------------------|-------------------------|---------|-------------------------|-------------------------|---------|
| **N**                    | 208                     | 364                     | N/A     | 102                     | 95                      | N/A     |
| **Maternal Characteristics** |                         |                         |         |                         |                         |         |
| **Maternal Race**        |                         |                         | 0.52    |                         |                         | 0.99    |
| Black                    | 72 (35%)                | 114 (32%)               |         | 32 (31%)                | 29 (31%)                |         |
| White                    | 126 (61%)               | 219 (61%)               |         | 64 (63%)                | 60 (63%)                |         |
| Other                    | 10 (5%)                 | 25 (7%)                 |         | 6 (6%)                  | 6 (6%)                  |         |
| Maternal Age (yr)        | 27.3 ± 6.1 (28-22-32)   | 27.9 ±6.8 (28-22-33)    | 0.29    | 27.4 ±5.6 (27-24-31)    | 27.8 ±6.0 (29-23-32)    | 0.58    |
| Gravida                  | 2 (1-3)                 | 2 (1-3)                 | 0.57    |                         |                         | 0.76    |
| Parity                   | 2 (1-3)                 | 1 (1-3)                 | 0.07    | 2 (1-3)                 | 1 (1-3)                 | 0.34    |
| **Complications of Pregnancy** |                         |                         |         |                         |                         |         |
| Hypertension             | 26 (13%)                | 73 (20%)                | 0.02    | 12 (12%)                | 16 (17%)                | 0.31    |
| Antepartum hemorrhage    | 30 (14%)                | 40 (11%)                | 0.24    | 10 (10%)                | 12 (13%)                | 0.51    |
| Thyroid Disease          | 2 (1%)                  | 14 (4%)                 | 0.04    | 1 (1%)                  | 4 (4%)                  | 0.20    |
| Diabetes                 | 17 (8%)                 | 46 (13%)                | 0.09    | 8 (8%)                  | 9 (9%)                  | 0.68    |
| **Intrapartum Complications** |                         |                         |         |                         |                         |         |
| FHR Decelerations        | 153 (74%)               | 282 (78%)               | 0.23    | 74 (73%)                | 74 (79%)                | 0.32    |
| Cord Prolapse            | 37 (18%)                | 49 (13%)                | 0.16    | 23 (23%)                | 16 (17%)                | 0.32    |
| Uterine Rupture          | 29 (14%)                | 22 (6%)                 | 0.001   | 16 (16%)                | 3 (3%)                  | 0.003   |
| Maternal Pyrexia         | 21 (10%)                | 41 (11%)                | 0.64    | 12 (12%)                | 9 (9%)                  | 0.60    |
| Antibiotics for suspected maternal infection | 38 (18%) | 85 (25%) | 0.08 | 22 (22%) | 22 (24%) | 0.76 |
| Shoulder Dystocia        | 20 (10%)                | 29 (8%)                 | 0.49    | 11 (11%)                | 6 (6%)                  | 0.26    |
| Placental Problem        | 52 (25%)                | 80 (22%)                | 0.41    | 22 (22%)                | 23 (24%)                | 0.66    |
| Maternal hemorrhage      | 14 (7%)                 | 55 (15%)                | 0.003   | 6 (6%)                  | 13 (14%)                | 0.06    |
| Maternal trauma          | 1 (0%)                  | 2 (1%)                  | 1.0     | 0 (0%)                  | 0 (0%)                  | N/A     |

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|                      | IH Trial (all patients) | OC Trial (all patients) | P-value | IH Trial (33.5 × 72hrs) | OC Trial (33.5 × 72hrs) | P-value |
|----------------------|-------------------------|-------------------------|---------|-------------------------|-------------------------|---------|
| Maternal cardiorespiratory arrest | 2 (1%)                  | 4 (1%)                  | 1.0     | 0 (0%)                  | 1 (1%)                  | 0.48    |
| Maternal seizures    | 1 (0%)                  | 5 (1%)                  | 0.42    | 0 (0%)                  | 1 (1%)                  | 0.48    |
| Rupture of membranes: |                         |                         |         |                         |                         |         |
| None                 | 0 (0%)                  | 97 (28%)                | 0 (0%)  | 28 (30%)                |                         |         |
| ≤8 hours             | 173 (92%)               | 216 (62%)               | 82 (91%)| 56 (61%)                |                         |         |
| >18 hours            | 15 (8%)                 | 38 (11%)                | 0.29†   | 8 (9%)                  | 8 (9%)                  | 0.96†   |
| Emergency C-Section  | 152 (73%)               | 231 (63%)               | 0.02    | 72 (71%)                | 61 (64%)                | 0.34    |
| **Neonatal Characteristics** |                      |                         |         |                         |                         |         |
| Gestational Age (weeks) | 38.9 ± 1.60             | 38.6 ± 1.46             | 0.06    | 39.0 ± 1.55             | 38.5 ± 1.45             | 0.03    |
| Male                 | 117 (56%)               | 212 (58%)               | 0.64    | 51 (50%)                | 52 (55%)                | 0.51    |
| Birthweight          | 3377 ± 630              | 3359 ± 599              | 0.73    | 3385 ± 617              | 3280 ± 528              | 0.06    |
| Length               | 50.8 ± 3.1              | 50.7 ± 3.0              | 0.61    | 50.6 ± 3.0              | 50.6 ± 2.8              | 0.98    |
| Head Circumference   | 34.1 ± 1.9              | 34.1 ± 1.8              | 0.93    | 34.4 ± 1.5              | 34.1 ± 1.5              | 0.16    |
| Outborn              | 93 (45%)                | 234 (64%)               | <0.0001 | 48 (47%)                | 59 (62%)                | 0.03    |
| Apgar score ≤5       |                         |                         |         |                         |                         |         |
| At 5 min             | 189 (91%)               | 306 (85%)               | 0.03    | 92 (91%)                | 79 (83%)                | 0.10    |
| At 10 min            | 154 (81%)               | 223 (69%)               | 0.004   | 80 (84%)                | 54 (69%)                | 0.02    |
| Cord Blood Gas       |                         |                         |         |                         |                         |         |
| ph                   | 6.86 ± 0.21             | 6.95 ± 0.19             | <0.0001 | 6.87 ± 0.19             | 6.94 ± 0.19             | 0.02    |
| Base deficit         | 19.2 ± 7.7              | 16.0 ± 7.3              | 0.0001  | 18.5 ± 6.7              | 15.7 ± 8.1              | 0.04    |
| Neonatal Blood Gas   |                         |                         |         |                         |                         |         |
| pH                   | 7.1 ± 0.2               | 7.1 ± 0.2               | 0.89    | 7.1 ± 0.2               | 7.1 ± 0.2               | 0.62    |
| Base Deficit         | 18.0 ± 7.7              | 17.2 ± 7.2              | 0.20    | 17.3 ± 6.9              | 17.2 ± 7.6              | 0.96    |
| Intubated at Delivery| 195 (94%)               | 286 (79%)               | <0.0001 | 97 (95%)                | 73 (77%)                | 0.0002  |
| Continued Resuscitation at 10 min (Y/N) | 195 (94%)               | 315 (87%)               | 0.01    | 95 (93%)                | 82 (86%)                | 0.11    |
| Time to Spontaneous Respiration | <0.001                 |                         |         |                         |                         | 0.0002  |
| < 5 minutes          | 22 (11%)                | 115 (34%)               |         | 12 (12%)                | 33 (37%)                |         |
|                          | IH Trial (all patients) | OC Trial (all patients) | P-value | IH Trial (33.5 × 72hrs) | OC Trial (33.5 × 72hrs) | P-value |
|--------------------------|-------------------------|-------------------------|---------|-------------------------|-------------------------|---------|
| 5 – 10 minutes           | 35 (18%)                | 76 (22%)                |         | 16 (16%)                | 15 (17%)                |         |
| >10 minutes              | 140 (71%)               | 150 (44%)               |         | 69 (71%)                | 41 (46%)                |         |
| Moderate Encephalopathy  | 134 (65%)               | 280 (77%)               | 0.002   | 69 (68%)                | 74 (78%)                | 0.13    |
| Severe Encephalopathy    | 73 (35%)                | 84 (23%)                |         | 32 (32%)                | 21 (22%)                |         |
| Seizures at Randomization| 94 (45%)                | 105 (29%)               | <0.0001 | 43 (42%)                | 27 (28%)                | 0.04    |
| Cooled prior to          | (N/A)                   | 252 (69%)               |         | (N/A)                   | 70 (74%)                | (N/A)   |
| randomization            | (N/A)                   | (N/A)                   |         | (N/A)                   | (N/A)                   |         |
| If yes – clinical cooling| (N/A)                   | 201 (80%)               |         | (N/A)                   | 52 (74%)                | (N/A)   |
| If yes – age cooling     | (N/A)                   | 3.9 ± 1.3               |         | (N/A)                   | 3.8 ± 1.3               | (N/A)   |
| Age at Randomization     | 4.3 ± 1.2               | 4.9 ± 1.2               | <0.0001 | 4.3 ± 1.3               | 5.1 ± 1.0               | <0.0001 |
| Age at Baseline          | 4.8 ± 1.3               | 5.1 ± 1.1               | 0.02    | 5.0 ± 1.2               | 5.2 ± 1.1               | 0.25    |
| Temperature at Baseline  | 36.9 ± 1.0              | 34.6 ± 1.8              | <0.0001 | 36.6 ± 1.0              | 34.3 ± 1.7              | <0.0001 |

P-values for categorical variables are from chi-square tests (or Fisher’s exact test for sparse data) and p-values for continuous variables are from T-tests, unless otherwise noted.

* P-values from Median two-sample test.

** This p-value compares >18 hours vs. No ROM or ≤18 hours.

a Includes use of ice packs, passive cooling, or clinical cooling (use of cooling device)
Table 2.

Variables reflecting care practices prior to and during TH

|                        | Induced Hypo Trial (33.5°×72hrs) N=102 | Optimizing Cooling (33.5°×72hrs) N= 95 | $^a$RR and 95% CI p-values |
|------------------------|----------------------------------------|----------------------------------------|---------------------------|
| **During First 72 hours (baseline>72 hrs)** |                                        |                                        |                           |
| Lowest PCO$_2$ (mmHG)  | 25.2 ± 6.4                             | 28.0 ± 7.5                             | $^b$ 0.08 (SE 1.09) 0.005 |
| Highest PO$_2$ (mmHg)  | 210.3 ± 119.1                          | 142.9 ± 106.4                          | $^b$ −82.7 (SE 18.3) <0.0001 |
| Lowest Glucose         | 66.1 ± 39.9                            | 60.5 ± 24.3                            | $^b$ −5.69 (SE 4.83) 0.24 |
| Highest Glucose        | 231 ± 124.9                            | 227.5 ± 141.4                          | $^b$ 4.19 (SE 19.2) 0.83  |
| **Prior to Baseline**  |                                        |                                        |                           |
| Intubated              | 92 (90%)                               | 74 (78%)                               | 0.85 (0.73-0.99) 0.04    |
| FiO$_2$                | 0.64 ± 0.30                            | 0.53 ± 0.31                            | −0.10 (SE 0.05) 0.03     |
| Inotropic Agent        | 32 (32%)                               | 25 (27%)                               | 0.95 (0.68-1.34) 0.79    |
| Anticonvulsants        | 49 (49%)                               | 25 (27%)                               | 0.58 (0.40-0.85) 0.005   |
| Analgesics/Sedatives   | 12 (12%)                               | 20 (22%)                               | 1.77 (0.95-3.31) 0.07    |
| **24 Hours**           |                                        |                                        |                           |
| Intubated              | 66 (67%)                               | 54 (58%)                               | 0.95 (0.74-1.22) 0.69    |
| FiO$_2$                | 0.57 ± 0.31                            | 0.42 ± 0.27                            | −0.15 (SE 0.05) 0.004    |
| Inotropic Agent        | 45 (47%)                               | 31 (34%)                               | 0.70 (0.46-1.05) 0.09    |
| Anticonvulsants        | 55 (55%)                               | 36 (38%)                               | 0.69 (0.47-1.01) 0.06    |
| Analgesics/Sedatives   | 31 (31%)                               | 52 (55%)                               | 1.86 (1.21-2.86) 0.005   |
| **48 Hours**           |                                        |                                        |                           |
| Intubated              | 49 (53%)                               | 44 (47%)                               | 0.95 (0.69-1.31) 0.75    |
| FiO$_2$                | 0.53 ± 0.31                            | 0.40 ± 0.25                            | −0.13 (SE 0.05) 0.01     |
| Inotropic Agent        | 37 (40%)                               | 25 (27%)                               | 0.71 (0.50-1.02) 0.06    |
| Anticonvulsants        | 45 (47%)                               | 31 (33%)                               | 0.72 (0.50-1.05) 0.08    |
| Analgesics/Sedatives   | 25 (26%)                               | 44 (47%)                               | 1.85 (1.23-2.79) 0.003   |
| **72 Hours**           |                                        |                                        |                           |
|                         | Induced Hypo Trial (33.5°×72hrs) N=102 | Optimizing Cooling (33.5°×72hrs) N=95 | aRR and 95% CI p-values |
|-------------------------|----------------------------------------|-------------------------------------|------------------------|
| Intubated               | 45 (50%)                               | 36 (40%)                            | 0.88 (0.61-1.27) 0.49  |
| FiO2                    | 0.50 ± 0.32                            | 0.40 ± 0.22                         | −0.08 (SE 0.06) 0.15  |
| Inotropic Agent         | 27 (31%)                               | 23 (26%)                            | 0.89 (0.53-1.49) 0.65 |
| Anticonvulsants         | 39 (41%)                               | 25 (27%)                            | 0.74 (0.49-1.14) 0.17 |
| Analgesics/Sedatives    | 18 (19%)                               | 35 (38%)                            | 2.03 (1.24-3.31) 0.005 |

a Results are from generalized estimating equations (GEE) regression (log-binomial), adjusted for level of HIE and intracenter correlations. Induced hypothermia (IH-cooled) is the reference group.

b Results are estimated differences in means, from linear regression adjusted for level of HIE and center as a random effect. Induced hypothermia (IH-cooled) is the reference group.

c Reflects intubation (high frequency ventilation or intermittent mandatory ventilation) and FiO2 at baseline.
Table 3.
Hospital, Discharge, and 18-22 Month Outcomes

|                           | Induced Hypothermia (33.5°×72hrs) N=102 | Optimizing Cooling (33.5°×72hrs) N= 95 | Unadjusted RR (95% CI), P-value | Adjusted RR, (95% CI), P-value |
|---------------------------|----------------------------------------|----------------------------------------|---------------------------------|-------------------------------|
| Length of Stay (days)     | 17.1 ± 15.0                            | 20.5 ± 15.6                            | 3.45 (SE 2.18), 0.12            | b 4.25 (SE 2.21), 0.06        |
| Gavage or Gastrostomy Tube| 15/81 (19%)                            | 18/87 (21%)                            | 1.12 (0.60 – 2.07), 0.72        | 1.07 (0.55 – 2.09), 0.83      |
| Discharge on Anticonvulsants| 31/81 (38%)                         | 21/87 (24%)                            | 0.63 (0.40 – 1.00, 0.052)       | 0.71 (0.38-1.31), 0.27        |
| Death in Hospital         | 19 (19%)                               | 7 (7%)                                 | 0.40 (0.17 – 0.90), 0.03        | 0.46 (0.17-1.27), 0.13        |
| Death by 18 months        | 24 (24%)                               | 8/93 (9%)                              | 0.37 (0.17 – 0.77), 0.009       | 0.38 (0.14 – 1.05), 0.06      |
| Moderate HIE              | 9/69 (13%)                             | 4/72 (6%)                              | 0.43 (0.14 – 1.32), 0.14        | 0.41 (0.13 – 1.36), 0.15      |
| Severe HIE                | 15/32 (47%)                            | 4/21 (19%)                             | 0.41 (0.16 – 1.06), 0.06        | 0.43 (0.15 – 1.24), 0.12      |
| Death or Disability       | 45 (44%)                               | 27/92 (29%)                            | 0.67 (0.45 – 0.98), 0.04        | 0.73 (0.47 – 1.15), 0.17      |
| Moderate HIE              | 22/69 (32%)                            | 14/71 (20%)                            | 0.62 (0.35 – 1.11), 0.11        | 0.62 (0.34 – 1.14), 0.13      |
| Severe HIE                | 23/32 (72%)                            | 13/21 (62%)                            | 0.86 (0.58 – 1.28), 0.46        | 0.86 (0.56 – 1.32), 0.49      |
| Cerebral Palsy            | 19/77 (25%)                            | 16/85 (19%)                            | 0.76 (0.42-1.38), 0.37          | 0.79 (0.50-1.24), 0.31        |
| GMFCS                     | N=77                                   | N=79                                   | c 0.35                         | N/A                           |
| Normal                    | 55 (71%)                               | 64 (81%)                               |                                 |                               |
| Level 1                   | 6 (8%)                                 | 2 (3%)                                 |                                 |                               |
| Level 2                   | 2 (3%)                                 | 2 (3%)                                 |                                 |                               |
| Level 3                   | 1 (1%)                                 | 3 (4%)                                 |                                 |                               |
| Level 4                   | 5 (6%)                                 | 0 (0%)                                 |                                 |                               |
| Level 5                   | 8 (10%)                                | 10 (10%)                               |                                 |                               |

a. Results are from GEE regression (log-binomial) adjusted for level of HIE and intracenter correlations. IH group is the reference group.

b. Results are estimated differences in means from linear regression adjusted for level of HIE and center as a random effect.

c. Cochran-Armitage trend test