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Developmental surveillance outcomes after therapeutic hypothermia for neonatal hypoxic ischemic encephalopathy by simplified office based tools

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Abstract

Objectives: Therapeutic hypothermia (TH) is considered standard of care for neuroprotection in newborn infants with hypoxic ischemic encephalopathy (HIE), either as selective head cooling (SHC) or whole-body cooling (WBC). Developmental surveillance (DS) is used for monitoring high risk children for identifying infants at risk for developmental delay. This retrospective, sequential cohort study compared DS outcomes of infants with HIE managed by TH with infants managed supportively on normothermia, by simplified office based screening tools.

Methods: DS evaluation was done in 93 infants with suspected HIE treated with either selective head cooling (SHC; n=22) or whole body cooling (WBC; n=44) and were compared with normothermic controls (n=27). DS were performed at 0-6, 6-12 and 12-18 months of age with classification as normal (without functional deficit), mild to moderately impaired (functional deficits in 1-2 developmental domains), and severely impaired (global functional deficits) by developmental screening assessments based on 'Center for Disease Control' (CDC) compendium. Neurological evaluation by pediatric neurologists aided the overall assessments.

Results: Normal DS scores were significantly higher in HIE infants treated with TH versus controls, 41% vs.15%; p=0.04, 45% vs.17%; p=0.04, and 49% vs. 19%; p=0.04 at 0-6, 6-12 and 12-18 months respectively. Severe functional impairments were significantly less frequent for infants who received TH. Additionally, amongst the infants treated with TH, there were less severe impairments in WBC versus SHC managed infants.

Conclusions: This study corroborates the efficacy of TH in preventing neurodevelopmental milestone impairments, especially severe dysfunction in infants with HIE utilizing surveillance tools and neurological evaluation.

Keywords: (MeSH): hypoxia-ischemia, brain, body cooling, head cooling, hypothermia, induced, developmental surveillance

Introduction

Therapeutic hypothermia, in the form of selective head cooling (SHC) or whole body cooling (WBC), has become the standard of care for neuroprotection in term and late preterm neonates ≥36 weeks' gestation with suspected hypoxic ischemic encephalopathy (HIE) [1-6].Edwards and colleagues, after evaluation of the Cool Cap (SHC), National Institute of Child Health and Human Development (NICHD; WBC), and TOBY (WBC) trials, demonstrated moderate hypothermia was neuroprotective, with a reduction in mortality and moderate-severe disability and an increase in disability-free survival, particularly in infants exhibiting moderate encephalopathy [7]. Meta-analysis by Taginet et al. of 7 studies showed that cooling is effective in improving survival and neurodevelopmental outcomes in newborns with moderate to severe HIE. Both approaches to therapeutic hypothermia were found to be effective in treating newborn infants with HIE [8]. A 2013 Cochrane systematic review further corroborated the neuroprotective aspects of TH [9]. Although both TH modalities have shown benefit with improved neurodevelopmental outcome, WBC is being used more frequently because of the ease of use and the ability to perform continuous EEG during cooling [7].

The post-hospital care for these infants is extremely important for the primary care pediatrician, developmental pediatrician and the pediatric neurologists. Standardized developmental screening is helpful for early identification of

children with developmental delays. Primary care pediatricians routinely follow developmental screening guidelines for normal children to identify children with developmental delay. However, at risk infants need 'developmental surveillance' with easy to use, validated and structured developmental screening protocol for identifying infants with developmental delay earlier for instituting appropriate interventions in a timely fashion. Studies from India and Australia have explored different surveillance programs for their countries [10, 11]. The American Academy of Pediatrics (AAP) developed a policy statement for identifying infants and young children who have developmental delays and disorders [12]. Drotar et al. [13] published an excellent review on selecting developmental surveillance tools for guiding pediatricians. However, there is no universally accepted screening tool appropriate for all populations and all ages. Broad screening tools address various developmental domains including fine and gross motor skills, language and communication, problem solving-adaptive behavior, and personal-social skills. At our institution, we have adopted developmental screening assessments based on 'Center for Disease Control' (CDC) compendium for surveillance of 'at risk' infants [14].

We report neurodevelopmental surveillance data for our infants who were managed with TH (SHC and WBC) from 2009-2017 compared with pre-TH era infants (control group). This retrospective study explores the neuroprotective differences for WBC and SHC techniques for TH following HIE and the efficacy of TH in preventing neurodevelopmental impairments using simplified surveillance methodology.

Materials and Methods

This retrospective study includes data from medical records of term and late preterm neonates (≥36 weeks' gestational age) with moderate and severe HIE, born between 2008 and 2017, managed in our Level IV regional perinatal center and who were subsequently followed in our pediatric neurology clinic. Approval for this study and waiver of informed consent was obtained from the Institutional Review Board of the Albert Einstein College of Medicine. The study conformed to the ethical standards of the institutional responsible committee and the Helsinki Declaration of 1975, as revised in 2000. Ninety three infants were identified as having been diagnosed with HIE. Sixty six of the neonates (71%) were treated with TH {44/66, 66.6% with WBC and 22/66, 33.3% with SHC}. SHC was standard therapy from 2009 to 2013 and WBC became the primary mode for TH therapy from 2013 onwards in our NICU. Standard inclusion criteria were adopted for diagnosis of eligibility for and management of TH protocols from the Cool Cap and NICHD trials [2,5,6]. Inclusion criteria were: an Apgar score of 5 or less at 10 min after birth; a continued need for resuscitation, including endotracheal or mask ventilation at 10 min after birth; or severe acidosis, defined as pH less than 7·00 or a base deficit of ≥16 mmol/L in an umbilical cord blood sample or an arterial or venous blood sample obtained within 60 min of birth and birth weight ≥1800 grams. Modified Sarnat scoring was utilized to categorize moderate to severe encephalopathy (Sarnat 2 or 3) [15]. The neonatal neurological examination evaluated 10 components: level of consciousness (hyper alert, lethargic or obtunded, and stupor or comatose); activity (normal, decreased, or absent); muscle tone (normal, hypotonic, or flaccid); posture (mild distal flexion, strong distal flexion or intermittent decerebration, i.e. extension); deep tendon reflexes (overactive, overactive or decreased/absent); primitive reflexes such as suck (active, weak or absent), moro (exaggerated with low threshold, weak or incomplete on high threshold or absent), grasp (normal or exaggerated, weak or absent), tonic neck (slight, strong or absent); pupils (mydriasis/reactive, miosis/reactive or variable/unequal/fixed), respiration (regular, variable or irregular/apneic); heart rate (normal/tachycardia, bradycardia or variable); seizures (none, common/focal/multifocal or uncommon excluding decerebration). The clinical examination, done by an attending neonatologist was used to characterize infants into modified Sarnat stages as follows: Stage 1: hyper alert, normal tone and activity, exaggerated Moro, absence of autonomic dysfunction; Stage 2: lethargy, decreased activity, hypotonia, weak primitive reflexes, constricted pupils, bradycardia or periodic breathing; Stage 3: stupor, coma, decerebrate posture, absent spontaneous activity, flaccid, absent reflexes, and nonreactive pupils or apnea. The Sarnat stages 1, 2, and 3 correspond to mild, moderate, and severe encephalopathy. Stage 2 or 3 was considered to represent an abnormal neurologic examination. Exclusion criteria included major congenital abnormalities (including findings suggestive of chromosomal anomalies [e.g., trisomy13, 18], imperforate anus (only for SHC), head trauma or skull fracture resulting in intracranial hemorrhage, coagulopathy with significant active bleeding, and infant with birth weight < 1,800g. The Olympic Cool-Cap system^{R} was used for SHC and an automated Gaymar Medi-Therm III hypo, hyperthermia Machine (MTA7900)^{R} and an esophageal temperature probe (disposable – DP400CE)^{R} was used for WBC. Twenty-seven infants (29%), born prior to the hospital's initiation of TH program, comprised the control group. Prior to the introduction of therapeutic hypothermia intervention for HIE neonates, traditional treatment was limited to supportive care in the form of ventilation management, vasopressor administration, hemodynamic regulation, maintenance of normothermia, and seizure treatment.

Serial neurological examinations and developmental screening assessments performed by a pediatric neurologist were obtained from 6 to 18 months of age. Assessments included: measuring head circumference, assessing muscle tone (hypotonia and hypertonia), the quality of movements, and determining milestones in four domains (movement/physical development, language/communication, cognitive and social/emotional) based on family input of milestone attainment as outlined by the Center for Disease Control (CDC) milestone guidelines [14]. [https://www.cdc.gov/ncbddd/actearly/milestones/index.html]. Neurodevelopmental outcomes were

classified as either: normal (no functional deficits), mild to moderate (deficits in 1-2 developmental domains), or severe (global functional deficits) on follow up assessments. Groups were compared with regard to neurodevelopmental outcomes from 6 to 18 months of age.

Statistical Analysis

Two-tailed p-values were calculated, using the "N-1" Chi-squared test, to explore statistical significance was performed.

Results

The maternal and neonatal characteristics of HIE infants in the WBC, SHC, and normothermia (Control) groups are listed in **Table 1**. Infants treated with TH and controls did not differ significantly between groups for cord pH, Apgar scores (at 5 and 10 minutes), gestational age, asphyxia etiology, early neurological examination (Sarnat staging) and presence or absence of neonatal seizures. Follow up neurological and developmental surveillance from 6-18 months of age was done for 67 infants (72%). Six infants died in the first 3 months of life. Mortality and cognitive impairment outcome data are presented in **Table 2**.

Severe neurodevelopmental impairments were significantly less frequent for HIE infants who received TH than controls (9/49, 18% vs. 9/20, 45%, p = 0.02; 7/40, 18% vs. 9/18, 50%, p=0.009 and 5/35, 14% vs. 7/16, 44%, p=0.02 at 0-6 month, 6-12 and 12-18 month follow up respectively. Similarly, the better outcomes (i.e., defined by normal development) in HIE infants following TH 20/49, 41% , 18/40, 45% and 17/35, 49% were higher than control cases 3/20,15% p=0.039, 3/18 17% p=0.04 and 3/16 19% p=0.04 30% at 0-6 month, 6-12 and 12-18 month follow up respectively **(Table 3).**

Additionally, amongst the TH treated infants, there was a trend for less severe impairments after WBC 4/32 13%, 3/26 12% and 2/22 9% than following SHC interventions 5/17, 29% p=0.14, 4/14 29% p=0.15 and 3/13 23% p=0.3 at 0-6 month, 6-12 and 12-18 month follow up respectively. Similarly there was a trend for good outcomes (i.e., normal development) across WBC 15/32, 47%, 13/26 50% and 12/22 55% as compared to the SHC treated infants 5/17 29% p=0.22, 5/14, 36% p=0.1 and 5/13 38% p=0.33 at 0-6 month, 6-12 and 12-18 month follow up respectively **(Table 4).**

Table 1. *Maternal and neonatal characteristics for infants underwent therapeutic hypothermia vs. Control.*

Characteristic	Selective Head Cooling (n=22)	Whole Body Cooling (n=44)	Normothermia (Controls) (n=27)	p value (¶SHC vs. Control)	p value (ŧ WBC vs. Control)
Gestational Age	38.2 ± 0.5	38.25 ± 0.4	37.6 ± 0.4		
Apgar 5 minute score					
0-3	11/22 (50%)	20/44 (47%)	10/25 (40%)	0.4961	0.5671
3-8	11/22 (50%)	24/44 (53%)	15/25 (60%)	0.4961	0.5766
Apgar10 minute score					
0-3	6/22 (27%)	10/44 (24%)	4/23 (17%)	0.4226	0.5117
3-8	16/22 (73%)	34/19 (76%)	19/23 (83%)	0.4226	0.5117
Gender					
Male	12/22 (54%)	18/44 (42%)	19/27 (70%)	0.2539	0.0227
Female	10/22 (45%)	26/44 (58%)	8/27 (30%)	0.2836	0.0227
Mode of Delivery					
C-section	8/22 (36%)	33/44 (75%)	11/27 (41%)	0.7236	0.0044
Vaginal Delivery	14/22 (64%)	11/44 (25%)	16/27 (59%)	0.7236	0.0044
Etiology					
Preeclampsia /Eclampsia	4/22 (18%)	2/44 (4%)	3/27 (11%)	0.4888	0.2542
Placental Abruption	1/22 (4%)	8/44 (18%)	3/27 (11%)	0.3700	0.4301
Other	9/22 (41%)	22/44 (50%)	11/27 (41%)	1.0	0.4637
Unknown	8/22 (36%)	12/44 (38%)	10/27 (37%)	0.9430	0.9332
Sarnat Score					
1	1/22(5%)	3/44(7%)	3/27 (11%)	0.4537	0.5606
2	18/22(81%)	38/44(86%)	21/27 (78%)	0.7984	0.3875
3	3/22 (14%)	5/44(11%)	3/27 (11%)	0.7533	1.0
Cord Blood pH					
≤7.00	10/22(45%)	19/44(43%)	11/27 (41%)	0.7806	0.7431
>7.00	12/22(55%)	25/44(57%)	16/27 (59%)	0.7806	0.7431
Seizures	6/22(28%)	8/44(18%)	8/27 (30%)	0.8794	0.2436
Prior cooling	3/22(14%)	4/44(9%)			
During Cooling	6/22(28%)	8/44(18%)			

Abbreviations: ¶SHC- Selective Head Cooling**, ŧWBC**-Whole Body Cooling

Table 2. *Mortality and cognitive impairment data in Therapeutic Hypothermia subjects: Whole body vs. Selective head cooling vs. Controls.*

Intervention	Assessment Age (months)	Mortality	Severe Cognitive Impairment	Mild/Moderate Cognitive Impairment	Good Outcome
Whole Body Cooling {WBC-44}	0-6 Follow up 32/44	2 (10%)	4 (12%)	11 (34%)	15 (47%)
	6-12 Follow up 26/44	0	3 (11%)	10 (38%)	13 (50%)
	12-18 Follow up 22/44	0	2 (10%)	8 (36%)	12 (55%)
Selective Head Cooling {SHC-22}	0-6 Follow up 17/22	2 (6%)	5 (29%)	5 (29%)	5 (29%)
	6-12 Follow up 14/22	0	4 (29%)	5 (23%)	5 (23%)
	12-18 Follow up 13/22	0	3 (23%)	5 (38%)	5 (38%)
Normothermia {Controls-27}	0-6 Follow up 20/27	2 (10%)	9 (45%)	6 (30%)	3 (15%)
	6-12 Follow up 18/27	0	9 (50%)	6 (33%)	3 (17%)

Table 3. *Neurodevelopmental surveillance outcomes data in infants (0-18 months) in Therapeutic Hypothermia subjects (Combined Whole body and Selective Head cooling) vs. Controls.*

Outcome	Assessment months	Therapeutic Hypothermia	Normothermia (Controls)	p value	95% CI
Severe Delay	0-6	9/49 (18%)	9/20 (45%)	**0.021**	3.8 to 49.3
	6-12	7/40 (18%)	9/18 (50%)	**0.009**	7.5 to 55.6
	12-18	5/35 (14%)	7/16 (44%)	**0.02**	4.4 to 54.3
Mild Delay	0-6	16/49 (33%)	6/20 (30%)	0.8	-21.7 to 23.8
	6-12	15/40 (37%)	6/18 (33%)	0.7	-22.4 to 26.9
	12-18	13/35 (37%)	6/16 (37%)	1.0	-25. to 27.6
Good Outcome	0-6	20/49 (41%)	3/20 (15%)	**0.039**	1.4 to 43.9
	6-12	18/40 (45%)	3/18 (17%)	**0.04**	1.2 to 46.7
	12-18	17/35 (49%)	3/16 (19%)	**0.04**	1.1 to 50

Table 4. *Developmental surveillance outcome data—whole body cooling vs. selective head Cooling.*

Outcome	Assessment months	Whole Body Cooling	Selective Head Cooling	p value	95% CI
Severe Delay	0-6	4/32 (13%)	5/17 (29%)	0.14	-5.2 to 41.8
	6-12	3/26 (12%)	4/14 (29%)	0.15	-6.2 to 45
	12-18	2/22 (9%)	3/13 (23%)	0.3	-11 to 41
Mild Delay	0-6	11/32 (34%)	5/17 (29%)	0.7	-22.4 to 28.5
	6-12	10/26 (38%)	5/14 (23%)	0.3	-15.6 to 38.9
	12-18	8/22 (36%)	5/13 (38%)	0.9	-27.2 to 32.8
Good Outcome	0-6	15/32 (47%)	5/17 (29%)	0.22	-10.6 to 41
	6-12	13/26 (50%)	5/14 (36%)	0.1	-10.9 to 57.6
	12-18	12/22 (55%)	5/13 (38%)	0.33	-15.8 to 44.6

Discussion

Studies and systematic reviews have demonstrated the efficacy of TH in preventing neurological deficits in neonates with HIE [3,7-9,16,17]. There are many excellent studies with full scale neuro-developmental evaluations available in the literature. Utility of developmental surveillance tools that can help identify infants at risk following HIE and help pediatricians to refer these infants for early intervention programs in a timely fashion are important. Easy to use tools can help primary care pediatricians monitor such infants in a systematic way. Our study utilized office based CDC milestone developmental screening guidelines and neurological examination by pediatric neurologists to validate these findings and provide new insight to follow up of HIE infants by pediatricians. These scoring systems are not a substitute for standardized, validated neurodevelopmental assessment tools.

Following our cohort from 6 to 24 months of age, it was revealed that severe neurodevelopmental impairments were significantly less frequent in infants treated with TH than controls. Zubcevic et al used 'Ages and Stages Questionnaire' (ASQ-3), another developmental surveillance tools and also reported promising results following TH [18]. Both therapeutic hypothermia modalities achieve brain cooling and have shown similar neurodevelopmental outcomes among surviving

children [19]. However, in our study, there were trends for less severe neurodevelopmental impairments after WBC than following SHC treatments despite no statistical differences in the entry criteria for TH. Whether there are subtle differences in neuropathology among infants treated with these two modalities has not been fully determined [14]. Studies suggest that brain MRIs are strongly predictive of neurological outcome in infants with HIE [14,20]. Sarkar et al. also identified more frequent MRI abnormalities in infants treated with SHC than with WBC (74% vs. 45%, p=0.0132), as well as more severe brain lesions in the SHC treated group (2 vs. 0, p=0.0014) [20].

The physiologic mechanism of this difference is not clear. However, it is possible that an uneven temperature gradient may exist across and within the cerebrum of SHC-treated infants, but not for infants treated with WBC as this approach is speculated to achieve more uniform cooling across all layers of the brain [21]. Does SHC potentially cause excessive brain cooling when the goal is to achieve moderate hypothermia? Wu et al suggested that brain temperature and brain–rectal temperature gradient were higher in neonates with severe encephalopathy than in those with moderate HIE during and after therapeutic hypothermia using WBC [22].

Despite the short term co-morbidities associated with TH, the benefits of cooling on survival and neurodevelopment outweigh the short-term adverse effects [8]. It might be expected that head cooling would produce a lower risk for adverse events than whole body cooling by limiting: a) the extent of systemic hypothermia, and b) the reduction in temperature (i.e., 34 to 35° core temperatures in SHC vs. 33.5 ± 0.5°C in WBC). However, the notion was not supported by data from studies [23,24]. Çelik et al. also compared whole body cooling to selective head cooling and found no difference in mortality, 12 months neurodevelopment follow up results or adverse events [25].

Some studies compared WBC and SHC interventions using distribution of lesions on MRI as a marker to predict long term outcomes in neonates [26,27]. These studies identified a significantly greater frequency of lesions in SHC infants, but there was insufficient data to suggest the lesions could be indicators of long-term neurodevelopmental outcomes [26]. A recent meta review, contrasting MRI lesion differences across hypothermia treated subgroups concluded that WBC yielded a better outcome than SHC by producing less neuroradiological evidence of cerebral injury [28].

Our study was constrained by a small sample size and therefore, several analyses suggesting group differences lacked sufficient statistical power to reach significance. Additionally, methodology was limited by using a simplified developmental surveillance and neurological examination rather than using standardized neurodevelopmental tools. Despite these limitations, this study reinforces the data on beneficial effects of TH and suggested a difference between cooling techniques that favored WBC. Simplified tools for developmental surveillance are helpful for pediatricians and pediatric neurologists in follow up TH treated HIE infants for an early identification of developmental delay and appropriate referral for an early intervention, if needed.

Conclusions

Therapeutic hypothermia (TH) has become a standard of care and should be instituted in term and late preterm infants with moderate-to-severe hypoxic ischemic encephalopathy. In our study severe neurodevelopmental impairments were significantly less frequent in HIE infants treated with TH than in those infants managed supportively (controls) between 6 and 18 months of age. TH with WBC provided better neurodevelopmental outcomes for HIE infants in this study. Standardized simple developmental surveillance tools are helpful in monitoring ‘at risk’ infants.

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