Original Research Article

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Effect of hypothermia for perinatal asphyxia on childhood outcomes

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ABSTRACT

Background: Perinatal asphyxia, neonatal asphyxia or birth asphyxia is the medical condition resulting from deprivation of oxygen to a new born infant that lasts long enough during the birth process to cause physical harm, usually to the brain. This study was performed to evaluate study population who were 6 to 8 years of age to determine whether the application of moderate hypothermia after perinatal asphyxia is associated with long term benefits.

Methods: This study was a randomised, controlled trials which consisted of infants who were admitted with moderate and severe encephalopathy within 6 hours after birth after an acute perinatal event, with acidosis or resuscitation. Infants were assigned to undergo whole body hypothermia at 33°C for 72 hours or to undergo usual care randomly.

Results: All maternal baseline characteristics and Neonatal characteristics are non significant in both groups. APGAR score ≤5 is significant at 10mins in comparison. cerebral palsy were 18% and 25%, respectively, the rates of blindness were 1% and 4% the rates of hearing impairment (requiring aids) were 5.4% and 12.8%. There were no significant between-group differences in the level of disability among all survivors or in motor function among the 45 nondisabled children. Among children who had moderate or severe disability at 18 months, the corresponding rates at 6 to 7 years of age were 88% in the hypothermia group and 95% in the control group. All the children who had moderate-to-severe cerebral palsy at 18 months continued to be affected at 6 to 7 years in both groups. There was no significant between-group difference with respect to IQ scores that were measured on a continuous scale and other scores, with the exception of 1 of the 11 scores compared (attention and executive function, P=0.03). There were also no significant differences between groups in mean scores on the index of health care status derived from parental assessments or in parental scores for children's strengths and difficulties and ADHD The mean difference in the academic achievement score favored the hypothermia group but was not significant.

Conclusions: Moderate hypothermia after perinatal asphyxia resulted in improved neurocognitive outcomes in middle childhood.

Keywords: Cerebral blood flow, Neonatal asphyxia, Perinatal asphyxia

INTRODUCTION

Perinatal asphyxia, neonatal asphyxia or birth asphyxia is the medical condition resulting from deprivation of oxygen to a new born infant that lasts long enough during the birth process to cause physical harm, usually to the brain. Hypoxic damage can occur to most of the infant's organs (heart, lungs, liver, gut, kidneys), but brain damage is of most concern and perhaps the least likely to quickly or completely heal. In more pronounced cases, an infant will survive, but with damage to the brain manifested as either mental, such as developmental delay or intellectual disability, or physical, such as spasticity. The primary causes of this condition are systemic hypoxemia and/or reduced cerebral blood flow (CBF) (see the image below). Birth asphyxia causes 840,000 or 23% of all neonatal deaths worldwide. It results most commonly from a drop in maternal blood pressure or

some other substantial interference with blood flow to the infant's brain during delivery. This can occur due to inadequate circulation or perfusion, impaired respiratory effort, or inadequate ventilation. Perinatal asphyxia happens in 2 to 10 per 1000 newborns that are born at term, and more for those that are born prematurely.1 WHO estimates that 4 million neonatal deaths occur yearly due to birth asphyxia, representing 38% of deaths of children under 5 years of age.² Perinatal asphyxia can be the cause of hypoxic ischemic encephalopathy or intraventricular hemorrhage, especially in preterm births. An infant suffering severe perinatal asphyxia usually has poor color (cyanosis), perfusion, responsiveness, muscle tone, and respiratory effort, as reflected in a low 5 minute Apgar score.³ Extreme degrees of asphyxia can cause cardiac arrest and death. If resuscitation is successful, the infant is usually transferred to a neonatal intensive care unit. For reducing the death risk or disability at 18 to 24 months of age and to enhance the survival rate free of disability, after delivery of the child, initiating moderate hypothermia of 33 to 35°C for 72 hours is necessary. The proportion of abnormalities in infants as observed on neuro-imaging process is reduced by hypothermia.⁴ The observations made on short term treatments are temporary, however early assessment of neurodevelopmental outcomes may be altered on follow-up later. Long term outcomes on neonatal hypothermia data is lacking.^{5,6} This study was performed to evaluate study population who were 6 to 8 years of age to determine whether the application of moderate hypothermia after perinatal asphyxia is associated with long term benefits.

METHODS

This study was a randomised, controlled trials which consisted of infants who were admitted in MES Medical College, Perinthalmanna during the period of November 2014 to October 2016. Inclusion Criteria were infants with moderate and severe encephalopathy within 6 hours after birth after an acute perinatal event, with acidosis or resuscitation. Infants were assigned to undergo whole body hypothermia at 33°C for 72 hours or to undergo usual care randomly. All children were evaluated at 6 to 8 years of age who were surviving. Written informed consent was taken from parents of all participants. To standardize all the procedures, a training session was given to research personnel. The primary outcome was death or IQ score of below 70 at age of 6 to 8 years, the secondary outcome was psychosocial health, severe cognitive delay, higher cognitive function, severe disability, disability of motor function.

Gross motor function classification system (GMFCS) was used for grading of functional activity.

- Level I: walking without restriction,
- Level II: walking without assistive mobility device,
- Level III: walking with an assistive device,
- Level IV: self-mobility with limitations,
- Level V: mobility severe limitation.

IQ scores were measured using primary intelligence scale III for children at or under 7 years and Intelligence scale IV in children of above 18 years of age. These two tests were combined to give a full scale IQ score which was classified as Normal if a mean score of (±SD) 100±15; Severe disability was considered in infants who had IQ score of more than 3 SD below the mean score (i.e. <55) or a GMFCS of IV or V. Moderate disability was considered in infants who had IQ score of 2 to 3 SD below mean score (i.e. 55 to 69) or a GMFCS level of III. Mild disability was considered in infants who had IQ score of 1 to 2 SD below the mean score (i.e. 70 to 84) or a GMFCS level of I or II. No disability is considered in infants who had IQ score of more than 84 (i.e. >1 SD below the mean).

Scoring on the Manual Ability Classification System is as follows: level 1, handles objects easily and successfully; level 2, handles most objects but with somewhat reduced quality or speed of achievement; level 3, handles objects with difficulty; needs help to prepare or modify activities; level 4, handles a limited selection of easily managed objects in adapted situations; level 5, does not handle objects and has severely limited ability to perform even simple actions

Parents and teachers, who were aware of study group assignments, completed the Strengths and Difficulties Questionnaire (on a scale of 0 to 40, with higher scores indicating more difficulties) and the Attention Deficit—Hyper activity Disorder (ADHD) Rating Scale IV (on a scale of 0 to 54, with higher scores indicating more severe symptoms). Appropriate translations were available for the all centers. Parents were also asked to complete questionnaires assessing their child's behavior, everyday memory, use of health care services, and demographic information and provided information about their child's health status

We obtained permission from parents to request information about educational attainment from the child's school. Teachers and parents then completed two detailed questionnaires the Total Academic Achievement Score19 and the Strengths and Difficulties Questionnaire (with the latter including responses from both teachers and parents) and provided information about any special educational needs.

RESULTS

This study involved 156 infants with moderate or severe encephalopathy who were assigned to undergo hypothermia at less than 6 hours (77 infants) or usual care (79 infants).

The follow up visits at 6 to 8 years of age were conducted over a period of November 2014 to October 2016. Out of 156 infants, primary outcome data was obtained from 144 enrolled in the study (92%), of which hypothermia group

(74 of 77 infants) which constitutes 96%, control group (70 of 79 infants) which constitutes 88%.

Table 1: Maternal baseline characteristics.

Characteristic	Hypothermia group (N=74)	Control group (N=70)			
Mother Age (in years)	26±5	26±5			
Caesarean delivery (Number %)	48 (65%)	52 (74%)			
Education less than high school (Number %)	22 (30%)	25 (36%)			
Complications during pregnancy					
Chronic hypertension	10 (14%)	11 (16%)			
Antepartum haemorrhage	8 (11)	17 (24%)			
Intrapartum complications					
Fetal heart rate deceleration	49 (66%)	48 (69%)			
Cord collapse	11 (15%)	7 (10%)			
Uterine rupture	9 (12%)	7 (10%)			
Shoulder dystocia	8 (11%)	6 (8.5%)			
Maternal haemorrhage	6 (8%)	9 (13%)			

All maternal baseline characteristics are non significant in both groups.

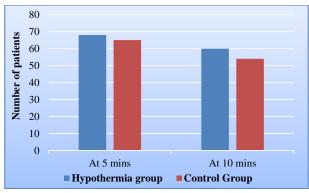
Intrapartum complications are not significant in both groups. Fetal heart rate deceleration is the most common Intrapartum complications observed in both groups.

Table 2: Neonatal characteristics.

Characteristic	Hypothermia group (N=74)	Control group (N=70)		
Age at randomization (hrs)	4.2±1.1	4.2±1.3		
Transferred from another hospital	35 (47%)	32 (45%)		
Males (no, %)	38 (51%)	48 (69%)		
Birth weight (gms)	3259±598	3278±557		
Intubation in the delivery room	70 (95%)	63 (90%)		
Cord blood pH	6.7±0.3	6.6±0.3		
Base deficit- mmol/liter	17.5±6.4	21.5±4.6		
Seizure (no, %)	31 (42%)	38 (54%)		
Encephalopathy (no, %)				
Moderate	51(68%)	39 (56%)		
Severe	22 (30%)	28 (40%)		

Neonatal characteristics are not significant

Among survivors at 6 to 7 years, in the hypothermia group and control group, the rates of cerebral palsy were 18% and 25%, respectively, the rates of blindness were 1% and 4% the rates of hearing impairment (requiring aids) were 5.4% and 12.8% (unadjusted P value for all comparisons, >0.05). The proportion of children with attention and executive function scores or visuospatial scores below 70 also did not differ significantly between the two groups.



APGAR score ≤5 is significant at 10mins in comparison.

Figure 1: APGAR score ≤5.

There were no significant between-group differences in the level of disability among all survivors or in motor function among the 45 nondisabled children. There were also no significant differences in parental assessments of the child's health or self-esteem between the two groups or in ratings of the emotional impact of the child's wellbeing on the parents.

Table 3: Pediatric assessment.

Variable	Hypotheri group	mia	Control gr	roup	P value		
	No./total no.	%	No./total no.	%			
Grade of disability							
No disability	45/74	60	29/70	41	0.001		
Mild disability	8/74	10.8	10/70	14			
Moderate disability	5/74	6.7	8/70	11.4			
Severe disability	10/74	14.2	15/70	21.4			
Moderate or severe disability	18/74	24.3	28/70	40	0.03		
Cerebral palsy	18/74	24.3	25/70	35.7	0.03		
Score on gro	Score on gross motor function classification system						
No abnormality	65/74	87	45/70	65.5	0.01		
Level 1–2	5/74	6.7	10/70	14			
Level 3–5	6/74	8.1	20/70	(28.5	0.15		
Score on ma	Score on manual ability classification system						
No abnormality	56/74	75.6	42/70	60	0.04		
Level 1–2	4/74	5.4	8/70	11.4			
Level 3–5	10/74	13.5	10/70	13.8	0.15		
Blindness	1/74	1.4	1/70	1.5	1.00		
Hearing impairment	4/74	5.4	8/70	12.8	0.15		

Among children who had moderate or severe disability at 18 months, the corresponding rates at 6 to 7 years of age were 88% in the hypothermia group and 95% in the

control group. All the children who had moderate-tosevere cerebral palsy at 18 months continued to be affected at 6 to 7 years in both groups.

Table 4: Psychometric assessment in study.

Psychometric assessment	Hypothermia group	Control group	P- value			
Intelligence						
Full-scale IQ score (Mean)	103.6±14.4	98.5±18.9	0.07			
Verbal IQ score (Mean)	105.2±15.6	101.1±17.3	0.16			
Nonverbal performance score (Mean)	101.1±15.0	96.7±19.0	0.12			
Processing speed score (Mean)	98.7±12.4	95.3±18.7	0.22			
Score on developmental neuropsychological assessment						
Attention and executive function (Mean)	9.6±2.1	8.6±2.7	0.03			
Memory and learning (Mean)	10.0±2.2	9.4±2.8	0.18			
Sensorimotor processing (Mean)	8.1±2.6	7.1±2.7	0.06			
Visuospatial processing (Mean)	10.4±3.1	9.6±3.5	0.17			

There was no significant between-group difference with respect to IQ scores that were measured on a continuous scale and other scores, with the exception of 1 of the 11 scores compared (attention and executive function, P=0.03). There were also no significant differences between groups in mean scores on the index of health care status derived from parental assessments or in parental scores for children's strengths and difficulties and ADHD The mean difference in the academic achievement score favored the hypothermia group but was not significant. The proportion of children who required use of special educational resources was lower in the hypothermia group than in the control group.

DISCUSSION

Children with asphyxial encephalopathy who were treated with hypothermia shortly after birth were significantly more likely to survive with an IQ score of 85 or higher at 6 to 7 years of age than were children who did not undergo such therapy. Similar proportions of children in the two groups died, but a higher proportion of survivors in the hypothermia group had an IQ score of 85 or higher, and the frequency of moderate-to -severe disability was lower in this group than in the control group.

We previously reported beneficial outcomes from treatment with hypothermia for neonatal hypoxicischemic encephalopathy at 18 to 22 months of age, including significant reductions in the rate of combined outcome of

death or moderate or severe disability. Other trials of whole-body or head-only cooling with whole-body hypothermia for neonatal encephalopathy have shown beneficial outcomes of hypothermia at 18 to 24 months of age in the entire study cohorts and in selected subgroups. In the present study assessing children at 6 to 7 years of age, the difference in rates of the composite outcome of death or an IQ score below 70 between hypothermia and usual care did not achieve statistical significance (P = 0.06); however, the previous finding of reduced mortality with hypothermia was maintained, with no appreciable increase in the risk of neurodevelopmental deficits among survivors.

Nondisabled children have delays in reading, spelling, arithmetic and language, memory, and sensorimotor perception scores, as well as increased rates of attention deficit hyperactivity disorder. ^{10,11} In the present study, we examined both gross and fine-motor outcomes to evaluate subtle benefits of hypothermia. We found a nonsignificant decrease (from 25% to 15%) in the rate of moderate or severe cerebral palsy in the hypothermia group as compared with the control group. We did not find a decrease in the risk of abnormalities in motor function among the non-disabled children in the hypothermia group as compared with those in the control group.

As reported here, there was no evidence of increased rates of an IQ score below 70, severe disability, or cerebral palsy at 6 to 7 years of age among surviving children treated with hypothermia; in our previous report, the frequency of ad-verse events was similar in the hypothermia and control groups both during the 72-hour study intervention period and during the neonatal-hospitalization period. ¹² In summary, whole-body hypothermia did not significantly reduce the rate of a composite end point of death or an IQ score below 70 at 6 to 7 years of age.

Shankaran S et al; previously reported early results of a randomized trial of whole-body hypothermia for neonatal hypoxic-ischemic encephalopathy showing a significant reduction in the rate of death or moderate or severe disability at 18 to 22 months of age. 12 Long-term outcomes are now available. In the original trial, we assigned infants with moderate or severe encephalopathy to usual care (the control group) or whole-body cooling to an esophageal temperature of 33.5°C for 72 hours. followed by slow rewarming (the hypothermia group). They evaluated cognitive, attention and executive, and visuospatial function; neurologic outcomes; and physical and psychosocial health among participants at 6 to 7 years of age. The primary outcome of the present analyses was death or an IQ score below 70. Of the 208 trial participants, primary outcome data were available for 190. Of the 97 children in the hypothermia group and the 93 children in the control group, death or an IQ score below 70 occurred in 46 (47%) and 58 (62%), respectively (P = 0.06); death occurred in 27 (28%) and 41 (44%) (P = 0.04); and death or severe disability occurred in 38 (41%) and 53 (60%) (P = 0.03). Other outcome data were available for the 122 surviving children, 70 in the hypothermia group and 52 in the control group. Moderate or severe disability occurred in 24 of 69 children (35%) and 19 of 50 children (38%), respectively (P = 0.87). Attention-executive dysfunction occurred in 4% and 13%, respectively, of children receiving hypothermia and those receiving usual care (P = 0.19), and visuospatial dysfunction occurred in 4% and 3% (P = 0.80). The rate of the combined end point of death or an IO score of less than 70 at 6 to 7 years of age was lower among children undergoing whole-body hypothermia than among those undergoing usual care, but significant. However. differences were not hypothermia resulted in lower rates and did not increase rates of severe disability among the survivors.

Azzopardi D et al; have conducted a study on newborns asphyxial encephalopathy who hypothermic therapy had improved neurologic outcomes at 18 months of age, but it is uncertain whether such therapy results in longer-term neurocognitive benefits.¹³ In this study, 325 newborns were randomly assigned with asphyxial encephalopathy who were born at a gestational age of 36 weeks or more to receive standard care alone (control) or standard care with hypothermia to a rectal temperature of 33 to 34°C for 72 hours within 6 hours after birth. They evaluated the neurocognitive function of these children at 6 to 7 years of age. The primary outcome of this analysis was the frequency of survival with an IO score of 85 or higher. A total of 75 of 145 children (52%) in the hypothermia group versus 52 of 132 (39%) in the control group survived with an IQ score of 85 or more (relative risk, 1.31; P = 0.04). The proportions of children who died were similar in the hypothermia group and the control group (29% and 30%, respectively). More children in the hypothermia group than in the control group survived without neurologic abnormalities (65 of 145 [45%] vs. 37 of 132 [28%]; relative risk, 1.60; 95% confidence interval, 1.15 to 2.22). Among survivors, children in the hypothermia group, as compared with those in the control group, had significant reductions in the risk of cerebral palsy (21% vs. 36%, P = 0.03) and the risk of moderate or severe disability (22% vs. 37%, P = 0.03); they also had significantly better motor-function scores. There was no significant be- tween-group difference in parental assessments of children's health status and in results on 10 of 11 psychometric tests. Moderate hypothermia after perinatal asphyxia resulted in improved neurocognitive outcomes in middle childhood.

Ambalavanan N et al; conducted a study to identify predictor variables and to develop scoring systems and classification trees to predict death/disability or death in infants with hypoxic-ischemic encephalopathy. Lecondary analysis of data from the multicenter, randomized, controlled, National Institute of Child Health and Human Development Neonatal Research Network

trial of hypothermia in hypoxic-ischemic encephalopathy was performed. Data for 205 neonates diagnosed as having hypoxic-ischemic encephalopathy were studied. Logistic regression analysis was performed by using clinical and laboratory variables available within 6 hours of birth, with death or moderate/severe disability at 18 to 22 months or death as the outcomes. By using the identified variables and odds ratios, scoring systems to predict death/disability or death were developed, weighting each predictor in proportion to its odds ratio. In addition, classification and regression tree analysis was performed, with recursive partitioning and automatic selection of optimal cutoff points for variables. Correct classification rates for the scoring systems, classification and regression tree models, and early neurologic examination were compared. Correct classification rates were 78% for death/disability and 71% for death with the scoring systems, 80% and 77%, respectively, with the classification and regression tree models, and 67% and 73% with severe encephalopathy in early neurologic examination. Correct classification rates were similar in the hypothermia and control groups. Among neonates diagnosed as having hypoxic-ischemic encephalopathy, the classification and regression tree model, but not the scoring system, was superior to early neurologic examination in predicting death/disability. The 3 models were comparable in predicting death. Only a few components of the early neurologic examination were associated with poor outcomes. These scoring systems and classification trees, if validated, may help in assessments of prognosis and may prove useful for riskstratification of infants with hypoxic-ischemic encephalopathy for clinical trials.

Eicher DJ et al; have done a study in which therapeutic hypothermia holds promise as a rescue neuroprotective strategy for hypoxic-ischemic injury, but the incidence of severe neurologic sequelae with hypothermia is unknown in encephalopathic neonates who present shortly after birth.11 This study reports a multicenter, randomized, controlled, pilot trial of moderate systemic hypothermia (33°C) vs normothermia (37°C) for 48 hours in neonates initiated within 6 hours of birth or hypoxic-ischemic event. The trial tested the ability to initiate systemic hypothermia in outlying hospitals and participating tertiary care centers, and determined the incidence of adverse neurologic outcomes of death and developmental scores at 12 months by Bayley II or Vineland tests between normothermic and hypothermic groups. Thirtytwo hypothermic and 33 normothermic neonates were enrolled. The entry criteria selected a severely affected group of neonates, with 77% Sarnat stage III. Ten hypothermia (10/32, 31%) and 14 normothermia (14/33, 42%) patients expired. Controlling for treatment group, outborn infants were significantly more likely to die than hypoxic-ischemic infants born in participating tertiary care centers (odds ratio 10.7, 95% confidence interval 1.3-90). Severely abnormal motor scores (Psychomotor Development Index <70) were recorded in 64% of normothermia patients and in 24% of hypothermia patients. The combined outcome of death or severe motor scores yielded fewer bad outcomes in the hypothermia group (52%) than the normothermia group (84%) (P = 0.019). Although these results need to be validated in a large clinical trial, this pilot trial provides important data for clinical trial design of hypothermia treatment in neonatal hypoxic-ischemic injury.

CONCLUSION

We found no significant between-group differences for many secondary outcomes assessed, including 10 of 11 psychometric test scores. Prioritizing assessment of IQ as the primary outcome meant that some other tests were curtailed if the assessor determined that the child could not maintain adequate performance. In conclusion, our study provides evidence that the benefits of moderate hypothermia after perinatal asphyxia persist into middle childhood.

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Ethical approval: The study was approved by the

Institutional Ethics Committee

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