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Original Article

Neurodevelopmental Outcome Following Therapeutic Hypothermia for Perinatal Asphyxia: A Cohort Study

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Abstract

Introduction: Therapeutic hypothermia is recommended for the treatment of neonates with hypoxic-ischemic encephalopathy. We conducted a cohort study to assess the neuroprotective benefits of therapeutic hypothermia by analyzing the survival and neurodevelopmental outcomes of neonates with moderate to severe HIE who underwent therapeutic hypothermia compared to those who did not.

Methods: Neonates with gestational age > 36 weeks and age < 6 hours with moderate to severe HIE were included in the study. Those who underwent therapeutic hypothermia according to a predefined criteria were assigned to the hypothermia group, while those who did not receive hypothermia served as the control group. Neurodevelopmental outcomes were assessed using the Ages & Stages Questionnaires (ASQ-3) at 3, 6, and 12 months of age.

Results: A total of 208 asphyxiated newborns were included in the study, with 100 in the therapeutic hypothermia group and 100 in the control group. Mortality was higher in the control group compared to the hypothermia group. Neurodevelopmental outcomes at 3, 6, and 12 months were significantly better in the hypothermia group compared to the control group.

Conclusions: Our study suggests that therapeutic hypothermia in term newborns with moderate to severe HIE is associated with improved survival and reduced neurologic sequelae. These findings support the implementation of therapeutic hypothermia as a standard treatment for neonates with perinatal asphyxia.

Introduction

Among term infants, hypoxic ischemic encephalopathy (HIE) due to acute perinatal asphyxia remains an important cause of neurodevelopmental deficits in childhood. Those newborns who have moderate encephalopathy have 10% risk of death. Those who survive have 30% risk of disabilities. In case of newborns with severe encephalopathy nearly 20% infants die and many survivors are handicapped.[1,2]

Therapeutic hypothermia (TH) is one of the management strategies that has been shown to reduce death and moderate to severe disability at 18 – 24 months in neonates with moderate to severe HIE.[3-6] The potential mechanisms of neuroprotection with TH includes inhibition of glutamate release, reduction of cerebral metabolism, which in turn preserves high energy phosphates, decrease in intracellular acidosis and lactic acid accumulation, reduction in nitric oxide and leukotriene production, prevents cerebral edema and inhibits apoptosis.[7,8] Six large randomized controlled trials demonstrated that whole body cooling decreases death and disability either in the entire cohort or within sub group of infants.[10-13]

There are limited studies reporting the effect of TH from Asian and African countries. Since TH has been introduced for the first time in our hospital in Nepal, this will be the first study done in Nepal to see the protective effect on neurodevelopmental outcome in survivors on long term follow up. The aim of the study is to observe and compare the neurodevelopmental outcome between neonates who received therapeutic TH and those who didn't based on clinical indications.

Methods

A hospital based prospective cohort study was conducted in the Neonatal Intensive Care Unit of Dhulikhel Hospital, Kathmandu University Teaching Hospital, Dhulikhel, Kavrepalanchowk, Nepal after receiving ethical approval from the Institutional Review Committee of Kathmandu University School of Medical Sciences with protocol approval number 5 / 20. The study population includes all neonates diagnosed with moderate and severe perinatal asphyxia. Neonates with gestational age > 34 weeks, with pH < 7 or base deficit > 16 mmol / L in an umbilical cord blood obtained within the first hour of birth, moderate or severe encephalopathy on clinical examination and APGAR score < 5 at 10 minutes after birth. Patients with mild birth asphyxia based on clinical examination and history, gestational age less than 34 weeks, and neonates with gross congenital anomalies were excluded. Upon admission to the NICU, neonates underwent urgent management including TH. TH was not assigned by the researcher but was a part of clinical management of neonates as per clinical criteria. Neonates presenting after 6 hours of life and those patients who presented during unavailability of cooling unit didn't receive TH. Based on exposure to TH, total 208 neonates were divided into two groups cases (104) and control (104). The target temperature for TH was 33.50C + 0.50C. TH was started within 6 hours of birth and continued for 72 hours, followed by slow rewarming over next 6 hours at the rate of 0.50C per hour. Core temperature was monitored continuously using an esophageal temperature probe during the cooling and rewarming phase. The esophageal probe was inserted and kept at the lower one third of the esophagus and it was sterilized after use. Information regarding antenatal care (ANC), perinatal events, resuscitation and other necessary information were noted. All major events in NICU, problems after initiating TH and vitals were recorded. The follow up visit records for long term outcome and neurodevelopmental outcome at 3, 6 and 12 months were included. The developmental assessment was done in a high – risk clinic and recorded using the same proforma used during the NICU stay. Descriptive statistics were used for description of the variables, means, medians, range and distribution of data. Chi square test was used to show significance of independent variables in relation to dependent (Neurodevelopmental outcome) which were compared at different ages using questionnaires based on the Ages & Stages Questionnaires (ASQ-3), appropriate for the age of the newborn in both therapeutic and non – therapeutic hypothermia groups. The study flow diagram is depicted in Figure 1.

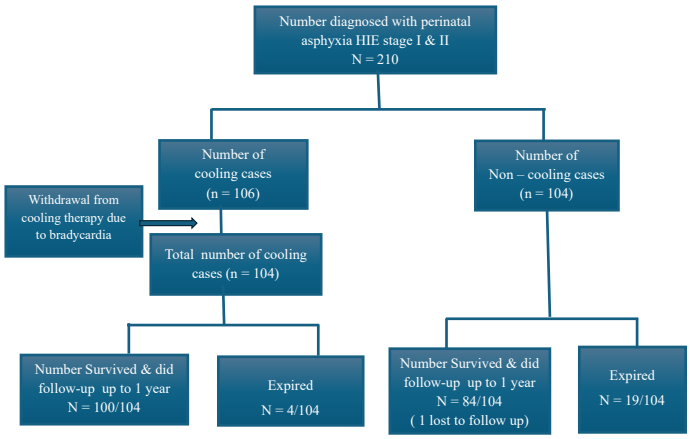

Figure 1: Study flow diagram of the research

Results

The study was conducted from March 2019 to April 2022 at the Neonatal Intensive Care Unit of Dhulikhel Hospital, Kathmandu University Teaching Hospital, Dhulikhel, Kavrepalanchowk, Nepal.

Neonatal characteristics (Table 1) were almost similar in both the groups, however prolonged seizures were observed in the control group. Resuscitation done was significantly more in the cooling group. The frequency of seizure activity was longer in the control group and the number of antiepileptic medications needed to control seizure were more in the cases group as compared to the cases (Table 2). Similarly, inotropes needed to maintain hemodynamic stability were lower in the cases (Table 3).

Table 1: Baseline characteristics of infant with perinatal asphyxia

	Cooling	Non – cooling	P – value
Sex			
Male	63 (47.01)	71 (52.99)	0.247
Female	41 (55.41)	33 (44.59)	
Period of gestation (Weeks)			
Mean	39.06	38.88	
Minimum – maximum	35 – 42	35 – 42	
Birth weight (Grams)			
Mean	2934.61	3206.01	
Min – max	2085 – 4150	2400 – 3300	
Onset of seizure (HOL)			
Mean	10.66	14.72	
Min – max	1 – 48	0 – 71	
Intubation	19	24	0.392
CPR	3	5	0.471
Resuscitation	100	89	0.008
Resuscitation			
Method of delivery	Required	Not required	Total
Normal	9 (7.14)	117 (92.86)	126
Caesarean section	9 (12.33)	64 (87.67)	73
Instrumental	1 (1.11)	8 (88.89)	9
Total	19 (9.13)	189 (90.87)	208

Table 2: Antiepileptics needed to control seizure

Drugs	Cases (104) (N) (%)	Control (104) (N) (%)
1	47 (72.72)	18 (27.27)
2	32 (49.21)	33 (50.79)
3	20 (33.89)	39 (66.10)
4	5 (26.31)	14 (73.68)

Table 3: Need of Inotropes among the cases and control

Inotropes used	Number	Percent
Cases	32	39.02
Control	50	60.98
Total	82	100

During NICU stay the most common complications (Table 4) were cerebral oedema (N = 123), bradycardia (N = 90), neonatal sepsis (N = 65) and NEC (N = 65). Except bradycardia all other complications were more common in the non - cooling group. Patients outcome, survival and age at testing according to categories of communication, gross motor, fine motors, problem solving and personal social skills for each of newborn treated with therapeutic hypothermia and controlled group for perinatal asphyxia at 3 months, 6 months, and 12 months age group are shown in Tables 6, 7 and 8.

Table 4: Complications during hospitalization

Comorbidities	Cases (N) (%)	Control (N) (%)	P – value
Neonatal sepsis	31 (47.69)	34 (52.30)	0.90
Hypoglycemia	2 (100)	0	0.23
Electrolyte imbalance	3 (30)	7 (70)	0.3
Shock	8 (62)	5 (38)	0.35
NEC	1 (20)	4 (80)	0.18
DIC	2 (33.33)	4 (66.66)	0.4
IVH	17 (34)	33 (66)	0.01
Cerebral edema	55 (44.75)	68 (55.23)	0.16
AKI	2 (33.33)	4 (66.66)	0.58
Bradycardia	75 (80)	15 (20)	< 0.001

Table 5 : Neurodevelopmental outcome at 3 months

Outcome	Cases	Control	P – value
Communication	97 (N), 2 (NN), 1 (BN)	72 (N), 2 (NN), 10 (BN)	< 0.001
Gross motor	97 (N), 1 (NN), 2 (BN)	72 (N), 2 (NN), 10 (BN)	
Fine motor	97 (N), 1 (NN), 2 (BN)	72 (N), 2 (NN), 10 (BN)	
Problem solving	96 (N), 2 (NN), 2 (BN)	72 (N), 1 (NN), 11 (BN)	
Personal social	96 (N), 2 (NN), 2 (BN)	72 (N), 0 (NN), 12 (BN)	
Expired	4	18	

Table 6: Neurodevelopmental outcome at 6 months

6 months	Cases	Control	P – value
Communication	96 (N), 3 (NN), 1 (BN)	72 (N), 0 (NN), 12 (BN)	< 0.001
Gross motor	97 (N), 2 (NN), 1 (BN)	72 (N), 0 (NN), 12 (BN)	
Fine motor	97 (N), 2 (NN), 1 (BN)	72 (N), 0 (NN), 12 (BN)	
Problem solving	96 (N), 3 (NN), 1 (BN)	72 (N), 0 (NN), 12 (BN)	
Personal social	96 (N), 3 (NN), 1 (BN)	72 (N), 0 (NN), 12 (BN)	
Expired	4	19	
N: Normal development, NN: Near normal, BN: Below normal			

Table 7: Neurodevelopmental outcome at 12 months

12 months	Cooling	Non – cooling	P – value
Communication	96 (N), 3 (NN), 1 (BN)	71 (N), 1 (NN), 12 (BN)	< 0.001
Gross motor	98 (N), 1 (NN), 1 (BN)	72 (N), 0 (NN), 12 (BN)	
Fine motor	97 (N), 2 (NN), 1 (BN)	71 (N), 1 (NN), 12 (BN)	
Problem solving	97 (N), 2 (NN), 1 (BN)	71 (N), 1 (NN), 12 (BN)	
Personal social	97 (N), 2 (NN), 1 (BN)	71 (N), 1 (NN), 12 (BN)	
Expired	4	19	
N: Normal Development, NN: Near Normal, BN: Below Normal			

Table 8: Stages of HIE vs immediate outcome

Stages of HIE	Survived (N) (%)	Expired (N) (%)	Total
Stage II	179 (92.27)	15 (7.73)	194
Stage III	7 (50)	7 (50)	14
P-value < 0.001			

We were able to assess the neurodevelopmental outcome for 184 babies using the ASQ – 3 questionnaires at different ages up to 1 year.

Death occurred in 4 (3.8%) babies in the cases and 19 (18%) babies in the control group. At 3, 6 and 12 months follow up development below normal was observed in 2 (1.9%), 1 (0.9%) and 1 (0.9%) in the cooling group compared with 10 (9.6%), 12 (11.5%) and 12 (11.2%) in the control group respectively. The death and disability were significantly less in the cases group in comparison to the control group.

Discussion

In this study, we share our experience with TH when used as a part of management for moderate to severe HIE. Published results of major randomized controlled studies have shown a beneficial effect of controlled TH on the survival and long-term neurological outcome for newborn who suffered from HIE.[13-16]

In this study recurrent seizures needing more than three antiepileptic drugs were (25) 24% in the cases while (53) 68% in the control group. Another Indian study also showed that the frequency of clinically observed seizure activity and the number of antiepileptic medications needed to control the seizure activity were significantly lower in cooling group in comparison to the non – cooling group.[17] Similar to this study, other studies done in two different parts of India also observed significant reduction in requirement of antiepileptic drugs, inotropes for cardiovascular instability and need of mechanical ventilation in the cooling group.[16,17]

The side effect related to perinatal asphyxia were similar for both groups; we observed low rates in pulmonary arterial hypertension in the protocol group compared to control group which is similar with the literature data.[18] Perinatal asphyxia can lead to systemic inflammation and oxidative stress, contributing to pulmonary vasoconstriction and endothelial dysfunction, which may result in pulmonary arterial hypertension (PAH). Perinatal asphyxia leads to increased pulmonary arteriolar vasoconstriction through hypoxia and acidosis, as well as the release of vasoconstrictor substances. When baby is in TH, it will decrease inflammation and oxidative stress which will decrease pulmonary vascular resistance.[19] Our analysis suggests that newborn of cooling group have reduced incidence of NEC. Another study has reported babies with HIE on cooling therapy have improved feeding tolerance and GI mortality compared with those in the non – cooling group.[20]

The present study showed that most subjects had bradycardia in the cooling group, which is an expected side effect of TH. Thoresen & WhiteLow have documented how HR and MAP changed in asphyxiated newborns during hypothermia and rewarming. In fact, while MAP increases, HR decreases during the TH and the opposite occurs during the rewarming.[21] Three randomized controlled trials have reported that decrease in HR was reversible.[12,14,21] There was no significant difference in renal injuries in both group in our study, although Roka et al suggested a beneficial effect of TH on several organs like kidney and liver.

Developmental outcome in this study was assessed by regular neurodevelopmental follow up examination and confirmed by the results obtained through ASQ – 3. The results were really encouraging in communication, problem solving, personal social, fine motor and gross motor with normal outcomes in

93% of babies in the cases as compared with 69% in control. Testing the reliability of ASQ – 3 in these conditions regarding the issues of sensitivity, specificity, positive predictive value, negative predictive value remains uncertain[22,23] but we had good correlation with having a clear structure.

A systematic review and metanalysis which had included 39 publications from 29 RCTs and 2926 participants showed that TH was associated with a significant reduction in mortality or disability at 18 – 24 months of age (10 studies, RR: 0.78:95% CI: 0.72 to 0.86).[24] Another meta – analysis states that it strongly supports the use of TH in newborns with HIE to reduce the risk of death and neurological impairment at 18 months.[25] In contrast, HELIX trial data suggests that TH does not reduce brain injury in MRI, nor improve the combined outcome of death or disability after neonatal encephalopathy in lower medium income countries but significantly increase the incidence of death relative to a control group.[26] Nowadays, few centers in Nepal have also started cooling therapy. Results from less developed countries may not always correlate with those in highly developed countries due to several reasons and for this problem we have to put particular emphasis on factors as maternal nutrition, scope of prenatal and perinatal infections, less developed medical transport service, late admission and lengthy decision making for Casesarean sections etc.

From the perspective of our limited experience, and first step in applying TH for perinatal asphyxia, we think that the results are highly promising. Our limitations including relatively small number of patients, single center study and short term follow up till only 12 months can restrict our conclusion yet can be solid base to start to assess the effects of TH in countries with limited health care resources.

Conclusions

Our study found that TH was linked to lower mortality and improved neurodevelopment at 3, 6, and 12 months, consistent with previous research. However, these findings warrant the need for larger, multicenter studies to explore long-term effects of TH on neurodevelopmental outcomes.

Conflict of Interest: None

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