Therapeutic Hypothermia in Moderate and Severe Hypoxic-Ischemic Encephalopathy: Use of Low-Cost vs High Technology Cooling Technique

Bhavana B. Lakhkar¹, Sachin Damake², Revat Meshram³, Shyam Lohia⁴, Sagar Karotkar⁵

¹Professor and HOD, Department of Neonatology and Pediatrics, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences (Deemed to be University), Sawangi(M) Wardha, Maharashtra, India; ²Professor and HOD, Department of Pediatrics, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences (Deemed to be University), Sawangi(M) Wardha, Maharashtra, India; ³Associate Professor, Department of Pediatrics, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences (Deemed to be University), Sawangi(M) Wardha, Maharashtra, India; ⁴Associate Professor, Department of Pediatrics, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences (Deemed to be University), Sawangi(M) Wardha, Maharashtra, India; ⁵Senior Resident, Department of Neonatology, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences (Deemed to be University), Sawangi(M) Wardha, Maharashtra, India.

ABSTRACT

Introduction: Birth asphyxia is a leading cause of death and neurodevelopmental problems in children. Perinatal insult is the common cause for brain injury and therapeutic hypothermia is said to be beneficial. State of the art equipment for hypothermia is costly and may not be available in institutions where birth asphyxia is common.

Aims and Objectives: To compare the effect of low-cost cooling techniques with high-cost cooling techniques in terms of morbidity and mortality and neurodevelopmental outcome at 12 months age.

Methods: All the term babies who present within 6-12 hours of birth and have moderate to severe encephalopathy will be recruited. Babies will be randomised for Low cost or high-cost cooling technique. Babies will be started on therapeutic hypothermia and will be monitored as per protocol. This will continue till 72 hours and then slow re-warming will be achieved. Any complications will be treated as per NICU protocol. Baby will be discharged when feeding is achieved and is vitally stable. Baby will be followed up until one year of age.

Outcome Measures: Death, duration of stay, neurological status at discharge and neurodevelopmental outcome at one year will be the outcome measures.

Key Words: Therapeutic hypothermia, Birth asphyxia, Neurodevelopmental

INTRODUCTION

Birth asphyxia leading to hypoxic-ischemic encephalopathy is one of the commonest cause of mortality and neuro-morbidity in infants in India. Acute perinatal insult to the brain is not a single event, it is an evolving process of cell death.¹ In the immediate period following insult primary energy failure (first 6 hrs after birth) occurs where there is depletion of oxidative metabolites leading to neuronal cell injury and toxic oedema. A large number of neurons die but many survive only to enter into the process of re-deterioration after a latent period.² This period during which secondary energy failure occurs is more severe and prolonged causing

permanent damage.³ The latent period so-called window of opportunity is the only period during which if proper action is taken the process of permanent damage can be partially halted with better survival and long term outcome.^{4,5}

Therapeutic hypothermia has been proved to be effective at least partially during this period. The cooling process is effective if started immediately (at least within 6 hours after birth) after the insult. Therapeutic hypothermia has been found to be useful in moderate and severe HIE secondary to perinatal asphyxia.⁴ It reduces mortality as well as long term neuro-morbidity. The high technology cooling may not be affordable for all patients and may not be available in all

Corresponding Author:

Dr. B. B. Lakhkar, Professor and HOD, Department of Neonatology and Pediatrics, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences (Deemed to be University), Sawangi(M) Wardha; Email: bhavanalakhkar53@gmail.com

ISSN: 2231-2196 (Print)

ISSN: 0975-5241 (Online)

Received: 25.08.2020

Revised: 14.10.2020

Accepted: 09.11.2020

Published: 30.11.2020

the hospitals. This study will compare outcome in patients with moderate to severe HIE using low-cost cooling technique and state of art high technology cooling apparatus. The patient selection criteria will be the same in both groups. The low-cost technique will be used in NICU of Department of Pediatrics, JNMC Sawangi (M) Wardha whereas high technology cooling will be used in NICU of the department of Pediatrics of Shree B. M. Patil Medical College Bijapur (Karnataka).

Patient selection criteria for both the groups will be the same and information gathered in the format also will be the same. Investigators from both institutes will share the data to make it collaborative study. A MOU will be made between both the institutes for the same.

Aim - To compare the outcome of moderate and severe HIE treated by low cost versus high technology cooling apparatus.

Primary Objectives

- 1 To record immediate mortality and neurodevelopmental outcome at one year of age in babies with moderate and severe HIE when low-cost technology for cooling is used.
- 2 To record immediate mortality and neurodevelopmental morbidity at one year age in babies with moderate and severe HIE managed with high technology cooling method.
- 3 To compare the above two in respect of mortality and neurodevelopment outcome at one year age.

Secondary objectives

1. To study difficulties while managing the patients especially in low technology cooling.
2. To study any side effects with any of the two methods.
3. To compare the outcomes with early treatment i.e. within six hours with late treatment (within 12 hours).

Study design: Prospective interventional comparative study.

Study setting: NICU of JNMC Sawangi(m) Wardha.

Subject: Patients with moderate to severe HIE in both the centres as per selection criteria.

Duration of study:

1. Case recruitment – one year
2. Follow up - one year.
3. Analysis -6months
4. Total – 2.5 years

Inclusion/exclusion criteria:

The first step will be ascertained criteria A and B. Second step is to confirm birth asphyxia (C) and then finally to confirm the severity of encephalopathy (D).

A. Gestation / Birth weight:

- i. Inborn neonates: 35 weeks/ $\geq$ 2kg
- ii. Out-born neonates: >2 kg (if gestation not known)

B. Age at presentation: For both inborn and Out-born neonates

- i. 6 hours since birth

C. Evidence of birth asphyxia:

Inborn neonates: Any one of the following:

1. Apgar score at 5 minutes < 5
2. Need for Intermittent positive-pressure ventilation (IPPV) till 5 minutes of birth
3. Cord arterial blood or blood obtained within 1h of birth pH < 7.0
4. Cord arterial blood or blood obtained within 1 h of birth base deficit > 16.0

Out-born neonates: Any one of the following:

1. Absence of cry at 5 minutes of age
2. Need for IPPV till 5 minutes of birth.^{10,11}

D. Staging of encephalopathy – For both inborn and out-born neonates

1. Anyone of the following:
 - i. Clinical seizures
 - ii. An altered state of consciousness (lethargy, stupor or coma) AND any one of the following:
 - a. Hypotonia
 - b. Abnormal reflexes including oculomotor or papillary abnormalities
 - c. Absent or weak suck

We will perform neurological examination hourly until 6 hours of age to ascertain if baby fulfils the eligibility criteria.

Exclusion criteria:

- 1) Babies with syndromes or anomalies including ano-rectal anomalies.
- 2) Babies with Major intracranial haemorrhage.
- 3) Denial of consent by parents.

Target cooling point will be 33° to 34.5° C and the total duration of cooling will be set at 72 hours. A patient fulfilling selection criteria will be recruited in the study within 6 to 12 of birth.

In NICU of Sawangi (M) Wardha, the patients will be managed as follows: Patient will be randomised for low cost or high-cost cooling technique.

Step I: The warmer will be put off and the rectal temperature of the baby will be taken every 30 minutes.

Step II:

- a) In babies randomised for low technique- If it has not reached the targeted temperature, cool packs will be

introduced wrapped in cloth one by one every 15 minutes till target temperature is reached with due precautions that none of the packs is frozen. After this temperature will be recorded at the 1 hour and if temperature maintained, the recording will be done every 2 hours. Always rectal temperature will be recorded and the target temperature will be maintained for 72 hrs.

b) In babies randomised for high-cost technique(Mera cradle). Baby will be managed in Mera cradle as per company instructions.

Step III: After 72hrs gradual rewarming of 0.5°C /hour will be done by removal of packs one by one. All patients will be monitored as per the following table 1.

Table 1: Medical Test Observation Chart

Parameter	Day 1	Day 2	Day 3	Day 4
Vitals Monitoring (Rectal temp, HR, RR) including blood pressure monitoring	Q 1 hr	Q 1 hr	Q 1 hr	1 hr x 6 hrs 3 hr after that
Neurological monitoring	Q 12 hr	Q 12 hr	Q 12 hr	Q 12 hr
Urine output	Q 6 hr	Q 6hr	Q 6 hr	Q 6 hr
ECG	Continuously	Continuously	Continuously	Continuously
Skin integrity	Q 6 hr	Q 6hr	Q 6 hr	12 hr
Investigation				
Glucose	Q 6 hr	Q 6hr	Q 6 hr	6 hr
Blood gas	Q 6 hr or as indicated by condition by baby	Q 12 hr or as indicated	Q 12 hr or as indicated	Once /24 hr then If indicated
Renal infection test	Once	Once	Once	once
Electrolytes	Once	Once	Once	once
Complete hemogram and bleeding parameters(Plt count, PT, APTT)	Only if required	Once	once	Once
Neurosonogram	If abnormal	If abnormal	If abnormal	If indicated

Rest of management will be as per NICU protocol. Details of baby, mother, resuscitation, examination findings, cooling procedure, rewarming procedure, investigation, morbidities till discharge will be entered in a pre-validated proforma.

Follow up

These patients will be followed up in the high-risk clinic. First, follow-up will be after 1 week and subsequent visits will be monthly till one year of age. Any mortality if occurs will be entered including the cause of death and age of the baby at death. The neurodevelopment of the baby will be closely monitored till one year of age. The outcome will be noted at the end of the year concerning development, neuro deficit, vision and hearing.

Statistical Analysis:

The outcome of babies will be compared by clubbing the data both the institutes. The results will be expressed as numbers and percentages or on average. Statistical analysis will be carried by. The difference between the two groups will be studied either by non-parametric Mann Whitney test for quantitative variables or by Chi-square test or Fischer exact for qualitative variables. Statistical difference of < 0.05 will

be considered significant.

Outcome measures-

Primary

- 1) Death in baby
- 2) Neurological status at discharge
- 3) Complications due to the technique used.
- 4) Duration of stay in NICU.
- 5) Neurodevelopmental outcome at 1 year age.

DISCUSSION

Several studies showed the benefit of controlled hypothermia in infants with perinatal asphyxia of acute onset. Its effect has not been proved in chronic hypoxia. Initiation of cooling before 6 hours of life for 72 hours has been found useful and adequate as longer duration is known to cause more harm and mortality. Effect of longer duration of cooling needs to be studied further.^{6,7} Most investigators used a target temperature between 32 °C to 34.5 °C. In India the most important problem faced was, asphyxia being more common in rural and remote areas. These are the areas with

more mortality and poor long term outcome but these mother find it difficult to reach a facility with the provision of therapeutic hypothermia. Transport facilities are poor and have no means of therapeutic hypothermia. Quality of transport will be a big issue in rural India. The key to therapeutic hypothermia remains the start of therapy within 6 hours of birth.⁵

Controlled therapeutic hypothermia reduced immediate mortality as well as long term neurological outcome⁶. Selective head cooling and total body cooling both are useful.^{7,8} Predictors of outcome also have been identified. Baby having severe encephalopathy at <6 hours, severe neuro deficit at 72 hours of hypothermia has poor prognosis.^{9,10} This indicates the importance of stage of encephalopathy while recruiting the cases. Though the therapy has to start before 6 hours of life, time to initiate cooling below 6 hours should not change at the cost of stabilization of neonate.^{9,11} Birth weight of baby also has some relation to cooling, lower weight babies respond better but need better blood pressure support.^{11,12}

There are not much safety issues with hypothermia, some coagulopathy may occur as hypothermia slows down the enzymatic activity of coagulation cascade and blood pressure support may be needed.¹³ Seizures may occur during rewarming. No other side effect has been noticed.⁹ Some adjuvants like Xenon gas and erythropoietin are under study. Better results after cooling therapy as compared to control has been shown in Neuroimaging also.¹⁴

CONCLUSION

Death, duration of stay, neurological status at discharge and neurodevelopmental outcome at one year will be the outcome measures.

REFERENCES

- Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG. Cooling for newborns with hypoxic-ischaemic encephalopathy. *Cochrane Database Syst Rev* 2013 Jan 31;2013(1):CD003311.
- Ness JK, Romanko MJ, Rothstein RP, Wood TL, Levison SW. Perinatal hypoxia-ischemia induces apoptotic and excitotoxic death of periventricular white matter oligodendrocyte progenitors. *Dev Neurosci* 2001;23(3):203-8.
- Gunn AJ, Thoresen M. Hypothermic neuroprotection. *NeuroRx* 2006;3(2):154-69.
- Vannucci RC, Towfighi J, Vannucci SJ. Secondary energy failure after cerebral hypoxia-ischemia in the immature rat. *J Cereb Blood Flow Metabol* 2004;24(10):1090-7.
- Maoulainine FM, Elbaz M, Elfaïq S, Boufrioua G, Elalouani FZ, Barkane M, et al. Therapeutic hypothermia in asphyxiated neonates: Experience from neonatal intensive care unit of University Hospital of Marrakech. *Int J Pediatr* 2017; 2017: 3674140.
- Gluckman PD, Wyatt JS, Azzopardi D, Ballard R, Edwards AD, Ferriero DM, et al. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: a multicentre randomised trial. *Lancet* 2005;365(9460):663-70.
- Zhou WH, Cheng GQ, Shao XM, Liu XZ, Shan RB, Zhuang DY, et al. Selective head cooling with mild systemic hypothermia after neonatal hypoxic-ischemic encephalopathy: a multicenter randomized controlled trial in China. *J Pediatr* 2010;157(3):367-72.
- Shankaran S, Laptook AR, Ehrenkranz RA, Tyson JE, McDonald SA, Donovan EF, et al. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. *New Eng J Med* 2005;353(15):1574-84.
- Shankaran S, Pappas A, McDonald SA, Laptook AR, Bara R, Ehrenkranz RA, et al. Predictive value of an early amplitude-integrated electroencephalogram and neurologic examination. *Paediatrics* 2011;128(1):e112-20.
- Shankaran S, Laptook AR, Tyson JE, Ehrenkranz RA, Bann CM, Das A, et al. Evolution of encephalopathy during whole-body hypothermia for neonatal hypoxic-ischemic encephalopathy. *J Paediatr* 2012;160(4):567-72.
- Azzopardi DV, Strohm B, Edwards AD, Dyet L, Halliday HL, Juszczak E, et al. Moderate hypothermia to treat perinatal asphyxial encephalopathy. *New Eng J Med* 2009;361(14):1349-58.
- Wyatt JS, Gluckman PD, Liu PY, Azzopardi D, Ballard R, Edwards AD, et al. Determinants of outcomes after head cooling for neonatal encephalopathy. *Paediatrics* 2007;119(5):912-21.
- Forman KR, Diab Y, Wong EC, Baumgart S, Luban NL, Masaro AN. Coagulopathy in newborns with hypoxic-ischemic encephalopathy (HIE) treated with therapeutic hypothermia: a retrospective case-control study. *BMC Paediatrics* 2014;14(1):1-6.
- Rutherford M, Ramenghi LA, Edwards AD, Brocklehurst P, Halliday H, Levene M, et al. Assessment of brain tissue injury after moderate hypothermia in neonates with hypoxic-ischaemic encephalopathy: a nested substudy of a randomised controlled trial. *Lancet Neurol* 2010;9(1):39-45.