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Original Research Article

Neurological assessment and immediate outcome of newborns treated with therapeutic hypothermia at tertiary care hospital of southern Rajasthan-a randomized control trial

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ABSTRACT

Background: Therapeutic hypothermia (TH) is standard-of-care for infants with moderate and severe HIE in developed countries; TH has been shown to decrease the risk of brain injury in asphyxiated newborns. Observations were like: 1) Asses morbidity and mortality in neonates with moderate and severe birth asphyxia treated with TH and 2) Asses neurological outcome in neonates.
Methods: A RCT was done in NICU of Balchikitsalaya, RNTMC, Udaipur. Phase changing material, FS 21, FS 29 used to provide TH for 72 hours, started within 6 hours of birth and neurological outcome was assessed.
Results: Total 60 neonates were enrolled 30 cases given TH and 30 control not given TH. Neurological assessment on basis of Thompson scoring, done on admission, 24, 48, 72 and 96 hours for both groups. At 48 hours, mean score in controls 14.5±1.67 and cases 11.47±2.34 ($p<0.05$). At discharge, mean score for controls was 11.31±3.67 and for cases was 5.24±2.72 ($p<0.005$). Mortality was 4 (13.3%) in cases and 11 (36.7%) in control group. Among 45 survivors, 25 (55.5%) required anticonvulsant at discharge; 15 from controls, 10 from cases group.
Conclusions: There was significant decrease in mortality in birth asphyxia babies given TH as compared to babies not given TH. Also, significant improvement in Thompson score among the cooled neonates at and after 48 hours of age suggestive of better immediate neurological outcome in these babies. Anticonvulsant's requirement was also significantly less in therapeutic hypothermia group.

Keywords: Birth asphyxia, HIE, Therapeutics hypothermia, Thompson score

INTRODUCTION

Out Of 136 million babies born every year, approximately 10% require some form of resuscitation at birth.[1] The neonatal mortality rate (NMR) as of 2018 is 22.7 per 1000 live births and intrapartum complications and birth asphyxia account for 20% of neonatal deaths globally and 19.2% of neonatal deaths in India. The reported incidence of deaths due to hypoxia varies from 2 to 16.2% in community-based studies, with case fatality rates ranging from 38.5% to 74%, WHO defines perinatal asphyxia as "failure to initiate and sustain breathing at birth".[2] It leads to multi-organ dysfunction. The neurological insult inherent to this clinical condition is referred as hypoxic ischemic encephalopathy (HIE). The primary cause being reduced cerebral blood flow.[3]

Perinatal Asphyxia refers to a condition during the first and second stage of labour in which impaired gas exchange leads to fetal acidosis, hypoxemia, and hypercarbia. Asphyxia may be suspected and HIE is included in the differential diagnosis when there is profound metabolic or mixed acidemia (pH<7.00) and base deficit ≥16 mmol/L in umbilical cord blood gases or

arterial blood gases within one hour of birth, first cry delayed >5 minutes, seizures within 12 to 24 hours of birth and burst suppression or suppressed background pattern on EEG or amplitude-integrated electroencephalogram (aEEG).[4]

Among the survivors of birth asphyxia, cerebral palsy and Neurological deficits are a dreaded complication associated with loss of potential productive member for the society and direct burden lasting for the entire life on the individual and family and social institutions. "Therapeutic hypothermia is standard-of-care for infants with moderate and severe HIE in developed countries and should be implemented within 6 hours after delivery, with timely referral to a centre with a hypothermia program as needed. Therapeutic hypothermia has been shown to decrease the risk of brain injury in newborns exposed to perinatal HI insult. Both total body and head cooling have been shown to be safe and effective and are recommended for treating newborns with moderate to severe hypoxia.[5]

Therapeutic hypothermia is neuroprotective by inhibiting several steps in the excitogenic oxidative cascade which include inhibiting the increase in the concentration of lactic acid, glutamate and nitric oxide in the brain. Moreover, TH inhibits protease activation, mitochondrial failure, free radical damage, lipid peroxidation and inflammation. TH has been shown to decrease brain energy use, prolong the latent phase, reduce infarct size, decrease neuronal cell loss, retain sensory motor function, and preserve hippocampal structures. Early application of TH preferably within 6 hours i.e., before the onset of the secondary phase of energy failure is likely to be effective and improve neurodevelopmental outcome. Usually, it is continued for a period of 72 hours for better neuro protection. Applying TH immediately or within a few hours after reperfusion and continued for 72 hours has been shown to favourably affect outcome in new born and adult animals. The mechanism is reduction of cerebral metabolism and prevention of edema HIE.[6]

Inadvertent excessive cooling (cold-injury syndrome) may occur during therapeutic hypothermia and may be due to inadequate monitoring, inexperienced staff or non-servo-controlled cooling systems. Asphyxiated newborns with HIE per se are known to have impaired thermoregulation. The effects of excessive cooling, especially pulmonary and cardiac dysfunction, are expected to be more serious in asphyxiated infants who already have multiorgan dysfunction, or the multi-organ dysfunction initially triggered by the HIE may be exaggerated by superimposed cold injury syndrome.

Aims and objectives

Aim and objectives of the study were: 1) to assess morbidity and mortality in term and near-term neonates suffering from moderate and severe birth asphyxia treated by therapeutic hypothermia, 2) Assessment of the immediate neurological outcome of these neonates and to compare with controls treated in normothermic environment and 3) To assess the side effects of therapeutic hypothermia if any.

METHODS

This study was a type of Randomised controlled trial study, which was done on term and near-term neonates with birth weight more than 2 kg with evidence of hypoxic ischemic encephalopathy admitted in NICU of Balchikitsalay, RNTMC, Udaipur, Rajasthan from July 2019 to June 2020.Controls were taken as neonates with similar presentation of hypoxia but they were treated in normothermic environment. Ethical clearance was provided by institutional ethics committee.

Inclusion criteria

All the neonates with gestational age>34 weeks, birth weight ≥2,000 gm brought to us within 6 hours of birth with moderate to severe birth asphyxia with 3/5 of the following criteria fulfilled and consenting for therapeutic hypothermia: 1) 10-minute Apgar score of ≤5, 2) Assisted ventilation initiated at birth and continued for at least 10 minutes, 3) pH ≤7.0 in cord blood ABG or pH of 7.01-7.15 in postnatal blood ABG obtained within first hour of life, 4) Base deficit ≥16 mmol/L in cord blood ABG or base deficit between 10 and 15.9 mmol/L in postnatal blood ABG obtained within first hour of life and 5) History of seizures or CNS abnormality s/o moderate to severe encephalopathy (assessed by modified Sarnat and Sarnat grading of HIE-at least 3/6 criteria).[7]

Exclusion criteria

All the neonates with gestational age<34 weeks, birth weight <2,000 gm brought to us with moderate to severe birth asphyxia will be excluded from the study if: a) Brought to the NICU after 6 hours of birth, b) Not consenting for the study, c) Presence of lethal chromosomal abnormality (e.g., trisomy 13 or 18), d) Presence of severe congenital anomalies (e.g., complex cyanotic congenital heart disease, major CNS anomaly, oesophageal atresia. Tracheoesophageal fistula, diaphragmatic hernia, imperforate anus, intestinal obstruction, exomphalos), e) Symptomatic systemic congenital viral infection (e.g., hepatosplenomegaly, microcephaly), f) Symptomatic systemic congenital bacterial infection (e.g., meningitis, DIC), g) Significant bleeding diathesis and h) Intracranial hemorrhage

The whole-body cooling was started in eligible babies within 6 hours of birth. The neonates were kept in the neonate cooler-The device uses phase changing material with 2 different melting point: PCM 21 with melting point at 21°C for induction phase and PCM 29 with the melting point at 29°C for maintenance phase.[9] In our study with PCM, induction time was approximately 45-90 minutes. We had to switch off the radiant warmer and

fix the rectal probe. We removed the PCM from refrigerator and keep it in room temperature for 30 minutes before commencing cooling. We used FS 21 and FS 29 for induction and once the target temperature was achieved, (~33.8) we removed FS 21 and use FS 29 for maintenance phase if nursery temperature was 27°C or above. If nursery temperature was 26°C or less, we used 29 FS for both the phases. If the infant's rectal temperature increased to 33.8°C, we changed 29 FS if it melted. If 29 FS was good, we added a 21 FS and then subsequently removed when the rectal temperature reached 33.5°C. If the temperature decreased to 33.2°C, we introduced a bed sheet between baby and FS. If temperature remained low, we turned on the warmer on manual mode at 20% till temperature reached 33.5°C.[10]

Neurological assessment by Thompson scoring was done on admission, 24 hours, 48 hours, 72 hours, 96 hours and at discharge for both groups. In this study, neurological assessment was done at regular intervals to assess the progress of each neonate with Thompson score. In the scoring system, a score of 0 is normal and the maximum score is 22 which signifies the worst possible status of HIE. Thompson scoring was graded as mild (Thompson score 1-10), moderate (11-14) and severe (>15).[8] Also, the requirement of antiepileptic drugs was assessed both by requirement during hospital stay as well as in at discharge. Primary outcome measurement was done in form of death or healthy discharge also and results were compared in both the groups.

Neonates were closely watched for complications of therapeutic hypothermia include bradycardia, cardiac arrhythmia, sudden cardiac arrest, thrombocytopenia, hypoglycemia, hypocalcemia, shock, sclerema and subcutaneous fat necrosis, acid-base and electrolyte disturbances, DIC, pulmonary hemorrhage, hemoconcentration, increased risk of infections due to impaired phagocytosis and leucocyte mobility etc.

Therapeutic hypothermia process was aborted prematurely in cases of persistent bradycardia of less than 80 beats per minute, thrombocytopenia of <1 lac/cumm, refractory shock, subcutaneous fat necrosis even after changing posture, disseminated intravascular coagulation leading to intracranial or pulmonary hemorrhage.

All the collected data managed and analyzed with standard software of biostatistics (SPSS version 2.0). Statistical analysis of the data was done with Chi-square test (for quantitative analysis), student t test (for continuous data) with assistance of qualified statistician. A $p<0.05$ was considered as statistically significant. Sampling technique used in study was purposive sampling (non-probability sampling).

RESULTS

Among the study population of 60 neonates with birth asphyxia, 30 were given therapeutic hypothermia and 30 were treated in a normothermic environment. Out of the 60 neonates, 45 (75%) neonates survived and 15 (25%) expired. In the case group which underwent therapeutic hypothermia, the mortality was only 4 (13.3%) neonates while the rest 26 (86.7%) survived. Whereas in the control group, there were 19 (63.3%) surviving neonates and 11 (36.7%) neonates expired (Table 3). There was a significant improvement in mortality scores in neonates with birth asphyxia kept given therapeutic hypothermia for 72 hours as compared to the asphyxiated neonates kept in a normothermic environment. The results were found to be statistically significant at $p<0.05$ ($p=0.0368$)

It was found that, at 24 hours, the mean Thompson score for controls was 15.27±1.68 and for cases was 14.8±2.02, with no statistical significance ($p=0.335$), thus signifying that there was no difference in the neurological status at 24 hours among the normothermic or hypothermic infants. At 48 hours, the mean score in controls was 14.5±1.67 and in cases was 11.47±2.34 and $p<0.05$ (Statistically significant). The same was found at 96 hours. Mean Thomson score for control group was 12.44+2.99 and case group was 6.93±2.803, with a $p<0.0059$ (Table 1) which was highly significant. There was a statistically significant ($p<0.05$) improvement in Thompson score seen among the cooled infants at and after 48 hours of age.

Neurological outcome was also assessed by requirement of antiepileptic drugs on discharge in the present study. A total of 23 neonates in control group required anti-epileptic drugs as compared to 15 in study group. This difference was found to be statistically significant. Among the surviving 45 neonates, 25 (55.5%) neonates required anticonvulsant at discharge; 15 neonates from the control group and 10 cooled neonates. 20 (44.4%) neonates did not require any AED on discharge. In the control group, out of a total of 19 surviving neonates, 15 (78.9%) neonates required AED on discharge. In the case group, 10 (38.4%) neonates received anticonvulsant on discharge. More number of babies in the control group required anticonvulsant at discharge (15 out of 19) as compared to the therapeutic hypothermia group where only 10 out of the surviving 26 cooled neonates were given oral anticonvulsant on discharge showing a higher requirement in neonates with birth asphyxia who did not receive 72 hours of whole-body cooling. The result was found to be statistically significant at a $p<0.05$ (Table 2).

Very few side effects were noticed during study. Only 4 babies in case group shown sinus bradycardia and 3 had some form of arrhythmias as compared to 1 baby in controls showing sinus bradycardia and also 1 showing some arrhythmias. This was not found statistically significant. Another side effect noticed was subcutaneous fat necrosis in 5 neonates of case group and none in controls. 9 and 7 babies developed hypotension (mean BP<40 mmHg) in study group and controls respectively. Persistent pulmonary hypertension was observed in 3 and

2 babies in both groups. Both the observations again were not statistically significant (Table 4).

Table 1: Neurological assessment of neonates with birth asphyxia and moderate to severe HIE.

Thompson scores (Hours)	Groups	Mean	p value
At 24	Case (TH)	14.8±2.024	0.335
	Control	15.27±1.680	
At 48	Case (TH)	11.47±2.345	<0.05
	Control	14.8±2.024	
At 72	Case (TH)	8.67±2.187	<0.05
	Control	13.54±2.411	
At 96	Case (TH)	6.93±2.803	<0.05
	Control	12.44±2.991	
At discharge	Case (TH)	5.24±2.721	<0.005
	Control	11.31±3.674	

Table 2: Requirement of antiepileptic drugs (AED).

AED	Groups		Total (%)	p value
	Cases (TH) (%)	Control (%)		
Not given at all	15 (50)	7 (23.3)	22 (44.4)	0.032
Given anytime	15 (50)	23 (76.6)	38 (55.5)	
At discharge not given	16 (61.5)	4 (21.1)	20 (44.4)	0.006
At discharge given	10 (38.4)	15 (78.8)	25 (55.5)	
Total	26 (100)	19 (100)	45 (100)	

Table 3: Outcome of neonates admitted with birth asphyxia and moderate to severe HIE.

Outcome	Cases (%)	Controls (%)	Total (%)	Significance
Death	4 (13.33)	11 (36.66)	15 (25)	0.0368
Discharge	26 (86.66)	19 (63.33)	45 (75)	
Total	30	30	60	

Table 4: Common observed side effects during study.

Side effects	Cases (%)	Controls (%)	Significance
Sinus bradycardia	4 (13.3)	1 (3.3)	Nil
Arrhythmias	3 (10)	1 (3.3)	Nil
Hypotension	9 (30)	7 (23.3)	Nil
PPHN	3 (10)	2 (6.7)	Nil

PPHN- Persistent pulmonary hypertension of newborn

DISCUSSION

Present study was randomized control trial which included 30 neonates with birth asphyxia, treated by therapeutic hypothermia by whole body cooling method for total duration of 72 hours. Similar numbers of controls were treated in normothermic environment. Two out of six studies, Gluckman et al, Zhou et al used selective head cooling to perform therapeutic hypothermia while Shankaran et al, Azzopardi et al, Thomas et al other studies used whole-body hypothermia similar to our present study.[10,12-14]

Observations revealed that immediate neurological outcome (first 24 hours) was almost similar in both groups, which was assessed by Thompson score done every 24 hours till 96 hours and then at discharge. At and after 48 hours till discharge, babies treated with therapeutic hypothermia revealed better results in form of low mean Thompson score every time, and results were found statistically significant. Quiet similar observations were seen by other authors. This can be explained due to prevention of damage to motor fibers and reticular activating system.

Outcome in form of persistent seizures requiring anti-epileptic drugs was better in study group as compared to controls probably due to neuroprotective action of therapeutic hypothermia increasing the seizure threshold.

Final outcome in form of discharged from hospital was also better in study group and was statistically significant. This could be explained due to prevention of end organ damage by therapeutic hypothermia which could have occurred, had whole body cooling not applied in time. Shankaran et al found a statistically significant effect on mortality.[12] Primary outcome data were among 205 infants was available. Death or moderate or severe disability occurred in 45 of 102 infants (44%) in the hypothermia group and 64 of 103 infants (62%) in the control group (risk ratio, 0.72; 95 percent confidence interval, 0.54 to 0.95; p=0.01). Twenty-four infants (24%) in the hypothermia group and 38 (37%) in the control group died (risk ratio, 0.68; 95 percent confidence interval, 0.44 to 1.05; p=0.08).

We observed few side effects in current study like sinus bradycardia, cardiac arrhythmias, hypotension, subcutaneous fat necrosis etc. A similar study was done by Thomas et a in their feasibility trial on whole body cooling in newborn infants with perinatal asphyxial encephalopathy in a low resource setting using phase changing material.[11] Adverse events observed during cooling were thrombocytopenia (25%), sinus bradycardia (25%), deranged bleeding parameters (20%), apo steatonecrosis (15%), hyperglycemia (15%), hypoglycemia (10%), hypoxemia (5%), life-threatening coagulopathy (5%) and death (5%). Similarly, mild edema, scleroderma or subcutaneous fat necrosis were reported in Gluckman et al, Shankaran et al and Zhou et

al during therapeutic hypothermia which recovered after rewarming.[11,13,15] It is recommended that regular skin assessment is needed to observe the infant's tolerance during hypothermia treatment. Frequent minimal turning is also recommended for infants undergoing therapeutic hypothermia to prevent pressure sores.

Limitations

Less number of cases as most of the babies we received from peripheral centers reached to us after 6 hours of birth so we could not start the therapy in those neonates and also, we could not perform amplitude EEG during hospital stay due to resource limitations.

CONCLUSION

After present study we could conclude that therapeutic hypothermia has emerged as very useful modality of treatment in neonates suffering from severe birth asphyxia due to its effect on improving neurological outcome, decrease susceptibility to neonatal seizures caused by hypoxic brain damage and also by improving overall survival. More multicentric studies need to be done to make any conclusive recommendations.

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