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Original Research Article

A randomized control trial on early open patient department-based assessment tool for prediction of neurological outcomes at the age of 1 month of life in asphyxiated neonates who underwent whole body cooling at tertiary care hospital in Southern Rajasthan

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ABSTRACT

Background: Therapeutic hypothermia (TH) is standard-of-care for infants with moderate to severe hypoxic ischemic encephalopathy (HIE) in developed countries. It should be implemented within 6 hours after delivery, and it has shown to significantly decrease the risk of brain injury in newborns exposed to perinatal hypoxemic ischemic insult with improved neurological outcomes. Objectives of the study were to assess early neurological outcome of neonates with moderate to severe birth asphyxia treated with TH.
Methods: A randomized control trial was done in NICU of Balchikitsalaya, RNT medical college, Udaipur, on neonates with evidence of grade II/III HIE. We used phase changing material-FS 21, FS 29 to provide whole body hypothermia for 72 hours within 6 hours of birth and observed the babies for early neurological outcome.
Results: A total of 60 neonates were enrolled in the study, 30 as cases, treated with therapeutic hypothermia and 30 as controls in normothermic environment. Neurological assessment was made on the basis of Thompson scoring and Ameil-Tison neurological assessment at term (ATNAT) at one month of age. We observed a better ATNAT score in TH group as compared to controls ($p<0.05$). Thompson score was significantly less in surviving neonates suggestive of better early neonatal outcome.
Conclusions: Statistically significant data suggestive of better early neurological outcomes were seen in the cases treated with 72 hours of hypothermia. These babies not only had lesser Thompson scores, but also showed better tone, and Improved ATNAT scores at 1 month of age, making this study important as an early marker of neurological injury/morbidity in later life.

Keywords: Birth asphyxia, HIE, TH, Thompson score, ATNAT 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 such as birth asphyxia accounts for 20% of neonatal deaths globally and 19.2% of neonatal deaths in India.[2] WHO defines perinatal asphyxia as "failure to initiate and sustain breathing at birth." Birth asphyxia triggers a cascade of events, primarily caused due to reduced cerebral blood flow and then reperfusion injury causing hypoxic ischemic encephalopathy which if not treated leads to neurological insult which at first is reversible,

and on crossing the latency period turns permanent, leading to severe neurological sequelae with high mortality and morbidity.[3]

Among the survivors of birth asphyxia, cerebral palsy and intellectual disabilities are a dreaded complication with loss of quality of life for both the child as well as the family members and a direct burden both financially and physically on the entire family and the society as a whole. The emotional turmoil faced by the caretakers due to prolonged hospitalizations, repeated visits only add to the pain and suffering in a country such as India which is still largely a developing nation with rural areas being the vast majority where proper ANC check-ups and safe delivery practices are scarce.

Perinatal asphyxia refers to all the inter and intrapartum conditions due to which there is impaired gas exchange which in turn leads to fetal acidosis, hypoxemia, and hypercarbia. HIE is one of the primary differentials when there is profound metabolic or mixed acidemia (pH<7.00) with base deficit ≥16 mmol/L in umbilical cord blood gases or arterial blood gases within one hour of birth, with the first cry delayed >5 min, early onset of seizures within 12 to 24 hours of birth and burst suppression or suppressed background pattern on EEG or amplitude-integrated electroencephalogram (aEEG).[4]

TH which includes both Total body and head cooling techniques has proven to be the standard-of-care for infants with moderate and severe HIE in developed countries. It is to be implemented within 6 hours after delivery, which can only be possible with a timely referral to a centre with a hypothermia facility. It has shown to decrease the risk of brain injury in new-borns exposed to perinatal HI insult.[5]

TH is neuroprotective by inhibiting several steps in the excitogenic oxidative cascade which include primarily 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 by reduction of cerebral metabolism and prevention of edema HIE has improved neurodevelopmental outcomes.[6]

Brain plasticity makes neurodevelopment and neurological assessment highly variable and difficult as effective predictors for future morbidities. However, there are a few scales which help us gauge the clinical severity immediately post birth using the Thompsons scoring system, Levenes' grading and modified Sarnat staging for neonatal encephalopathy. One such effective method which was used in this study was assessing the simple muscle tone of the infant on follow up and grade it according to the ATNAT. Adductor angles (40^o-80^o), popliteal angle (80^o-100^o) and dorsiflexion angles (60^o-70^o) along with scarf sign (elbow does not cross midline) was taken and compared with the normal values for neonates aged 0-3 months. Angles smaller than normal indicated hypertonia and larger than the normal values indicated hypotonia.[7] It was shown to be an effective, relatively easy and less cumbersome way of assessment at an early age as a predictor for morbidities in later life.

Aims and objectives

Assessment of the early neurological outcome at 1 month of age of asphyxiated Neonates with Moderate to Severe Hypoxic Ischemic Encephalopathy treated with therapeutic hypothermia within 6 hrs of birth in comparison with controls in normothermic environment.

METHODS

A randomised controlled trial was done on near-term and term neonates with birth weight more than 2 kg with evidence of moderate to severe hypoxic ischemic encephalopathy admitted in NICU of R.N.T. medical college, Udaipur, Rajasthan in the period between July 2019 to June 2020. Neonates with similar presentation of hypoxia treated in normothermic environment were controls for this study.

Inclusion criteria

All the neonates with gestational age ≥34 weeks, birth weight ≥2,000 gm within 6 hours of birth with evidence of moderate to severe birth asphyxia with 3/5 of the following criteria fulfilled and consenting for TH: 1)10-min Apgar score of ≤5, 2) Assisted ventilation initiated at birth and continued for at least 10 min, 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) H/O seizures or CNS abnormality s/o Moderate to severe encephalopathy (assessed by modified Sarnat staging for neonatal encephalopathy).[8]

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, D) Presence of severe congenital anomalies, 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.

TH as whole-body cooling was started in the cases within 6 hours of birth. The neonates were kept in the neonate cooler, a device which uses phase changing material (PCM) with 2 different melting points: PCM 21 with melting point at 21°C for induction phase and PCM 29 with the melting point at 29°C for maintenance phase.[10,11] In study induction time to reach desired temperature was approximately 45-90 min. Device was kept under radiant warmer and a rectal probe was fixed with all aseptic techniques to record and monitor core temperatures. Vitals for these neonates were continuously monitored.

The PCM were stored in the refrigerator and keep it in room temperature for 30 min 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 solid and did not soften, 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] After 72 hours of giving therapeutic hypothermia, gradual rewarming of babies was done over the period of 6-10 hours by increasing the temperature gradually by 0.5^0C every hour. Strict monitoring of vital parameters was done so as to detect any procedural complication at earliest.

Management of all vital parameters, seizures, electrolyte imbalances, ventilation and perfusion were done in accordance with the NICU policies. Meticulous charting of all activity via the Thompsons score and clinical assessment was done until discharge. Neonates were monitored daily for tone, seizures, apnea, need of anti-epileptics, inotropes, electrolyte corrections, renal impairment and ventilation perfusion mismatch. Once vitally stable and hemodynamically fit to discharge, they were followed up at 1 month of age. Anthropometry was taken and neurological assessment was done at one month of age. Weight was recorded using digital weighing scale. All the collected data was managed and analyzed with standard software of biostatics (SPSS version 21).

Length was recorded using infantometer. Head circumference was noted with measuring tape. General examination was done for skull shape, fontanelle and sensorium of baby was observed and complete systemic examination was performed. Neurological assessment was done by asking for any abnormal movements and history of convulsions. Motor functions was checked by range and symmetry of spontaneous movement. Muscle tone was checked on basis of ATNAT and results were compiled according to the AT angles found at 1 month of age.[9] Adductor angles (40^0-80), popliteal angle (80^0-100^0) and dorsiflexion angles (60^0-70^0) along with scarf sign (elbow does not cross midline) was taken as normal values for neonates aged 0-3 months. Angles smaller than the normal indicated hypertonia and larger than normal indicated hypotonia. Tendon jerks were noted, Moros's reflex, sucking, rooting responses were seen. Response to painful stimuli was noted as part of sensory examination. Neurological assessment by Thompson scoring was done on admission, during NICU stay, at discharge and at 1 month ofage for both groups. Thompson score comprises of 8 parameters like muscle tone, posture, seizure activity, consciousness, Moro reflex, grasp reflex, sucking, anterior fontanelle, and respiration. Here we compared it at 1 month of age. A score of 0 was considered 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).[9] Results were tabulated and compared to look for significance if any.

Table 1: Amiel-Tison neurological assessment at term.

Age (months)	Adductor angle	Popliteal angle	Dorsiflexion angle	Scarf sign
0-3	40^0-80^0	80^0-100^0	60^0-70^0	Table
4-6	70^0-110^0	90^0-20^0	60^0-70^0	Elbow crosses midline
7-9	110^0-140^0	110^0-160^0	60^0-70^0	Elbow goes beyond axillary line
10-12	140^0-160^0	150^0-170^0	60^0-70^0	

Table 2: Thompsons score for HIE.

Sign	0	1	2	3
Tone	Normal	Hypertonia	Hypertonia	Flaccid
Consciousness	Normal	Hyperalert, stare	Lethargic	Comatose
Fits	Normal	Infrequent <3 days	Frequent >2/day	
Posture	Normal	Fisting/cycling	Strong distal flexion	Decerebrate
Moro	Normal	Partial	Absent	
Grasp	Normal	Poor	Absent	
Suck	Normal	Poor	Absent±bites	
Respiration	Normal	Hyperventilation	Brief apnea	(Apnea)
Fontanelle	Normal	Full not tense	Tense	

(Maximum score 22 with worst prognosis and minimum score is 0 with best prognosis)

RESULTS

Among the study population of 60 neonates with birth asphyxia, 30 were neonates undergoing therapeutic hypothermia and 30 were treated in a normothermic environment. A total of 15 neonates expired during NICU stay, 4 from therapeutic hypothermia group and 11 from controls. Neurological assessment at 1 month age could be done in these 45 surviving babies.

Out of the 45 infants, 25 (55.5%) had a normal tone as assessed by ATNAT. Whereas 20 (44.4%) neonates had marked hypotonia. In the control group, out of a total of 19 surviving babies, 7 (36.8%) had a normal tone and 12 (63.3%) neonates had hypotonia. In group that was provided TH, only 8 (30.76%) neonates had hypotonia while rest 18 (69.23%) neonates had a normal neurological assessment according to ATNAT. Results were found statistically significant p<0.05, (p=0.03082).

Table 3: Neurological assessment of neonates with birth asphyxia and moderate- severe HIE using ATNAT-(at 1 month of age).

Tone	Control (%)	Case (TH)	Total (%)	P value
Normal tone	7 (36.8)	18 (69.2)	25 (55.5)	0.030
Hypotonia	12 (63.2)	8 (30.76)	20 (44.4)	
Total	19 (100)	26 (100)	45 (100)	

Table 4: Neurological assessment of neonates with birth asphyxia and moderate-severe HIE at 1 month of age using Thompson score.

Variables	Thompson score	Groups (%)		Total (%)	P value
		Controls	Cases (TH)		
Total score=22, (Best prognosis=0, worst prognosis=22)	1	0	7	7	<0.005
		0.00	26.90	14.89	
	2	0	11	11	
		0.00	42.30	23.40	
	3	5	7	12	
		23.80	26.90	25.53	
	4	6	1	7	
		28.57	3.80	14.89	
	5	5	0	5	
		26.31	0	11.11	
	6	3	0	3	
		15.78	0	6.66	
	>6	0	0	0	
		0.00	0	0.00	
Total	Number	19	26	45	
	%	100	100	100	

Score of 6 was seen in 3 (6.66%) neonates, all belonging to the control group. Five (11.11%) neonates had a score of 5/22, all these 5 were also from the control group. Making a total of 11 neonates having a Thompson score of ≥5, all from the normothermic group. A score of 4 was seen in 7 (14.89%) neonates in the study population, out of which 6(28.57%) were from the control group and 1 (3.80%) were from the case group. The 12 (25.53%) neonates had a score of 3/22. Out of these 12, there were 7 (26.9%) who had undergone therapeutic hypothermia, and 5 (23.80%) from the control group. The 11 (23.40%) neonates had a score of 2, all belonged to the hypothermia group. The 7 (14.89%) neonates had a Thompson score of 1/22, all from the case group. Thus, we see that all the neonates with a Thompson score of 2 and below belonged to the hypothermia group, indicating, a better neurological outcome at one month of age, in the TH intervention (p<0.005).

DISCUSSION

Our study was randomized control trial done in tertiary care teaching hospital of Southern Rajasthan which included 30 neonates with birth asphyxia, treated by therapeutic hypothermia by whole body cooling method for total duration of 72 hours. Similar number of controls were treated in normothermic environment. Gluckman et al used selective head cooling to perform therapeutic hypothermia while Shankaran et al, Azzopardi et al and Thomas et al other studies used whole-body hypothermia similar to our present study.[12-14]

Observations revealed that immediate neurological outcome was significantly better in study group as compared to controls in form of better survival, better neurological assessment scores, less requirement of antiepileptic drugs at discharge. In present study we

focused on early neurological outcome at 1 month of age. This assessment is very important as early markers of cerebral palsy can be seen clearly at this age, so that early intervention can be started to minimize future disabilities, neurological assessment at this age can best be done by assessing motor system by muscle tone, posture and neonatal reflexes.

Our study shown that early neurological outcome in therapeutic hypothermia group was significantly better as detected by neuromotor assessment at 1 month age by various method of scoring systems. Shankaran et al, found a statistically significant effect on, major disability among survivors; the rate of cerebral palsy was 19% in the hypothermia group as compared with 30 percent in the control group Azzopardi et al noted survival without disabilities was significantly higher in the cooled group compared with the usual care group.[12,14] The rate of CP was lower and improved mental and Psychomotor Indices were noted in the hypothermia group compared with the usual care group, all $p<0.05$).

Limitations

The total number of neonates enrolled could be stronger making the study more effective. We received cases of birth asphyxia from rural areas in the peripheries with poor connectivity and facility, wherein some reached after the cut-off time of 6 hours duration post birth. They were ruled out of the study groups.

Also, due to limited machinery and human resources, we did not have an amplitude EEG for these neonates wherein we could have picked up the non-convulsive seizures and treated accordingly, bettering the neurological outcome furthermore. Bedside cranial USG would have made daily USG and picking up of any Intraventricular hemorrhages better and the study more evidence based.

CONCLUSION

Concluding our present study on a very positive notes we found statistically significant data supporting the usage of TH as the standard of care for neonates with perinatal birth asphyxia with evidence of moderate to severe HIE as a way of improving early neurological outcome, and also by overall survival in a tertiary care centre of a government run facility in a developing country such as ours. More multicentric studies need to be undertaken so that we can find easily accessible centres for referral in multiple parts of the country to make a larger impact and also to make and improve conclusive recommendations.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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