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Original Research Article

Impact of therapeutic hypothermia (whole body cooling) on severely asphyxiated term neonates: a prospective non-randomized comparative study in an Indian tertiary care setting

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ABSTRACT

Background: Early application of Therapeutic Hypothermia within 6 hours of birth is neuroprotective. We aimed at examining whether therapeutic hypothermia alongside standard optimal intensive care improves immediate survival outcome and reduces neuro-disability.
Methods: This was a prospective non-randomized study involving inborn and out born newborns admitted at NICU, carried out from March 2022 to December 2022. Eligible candidates were enrolled as cases and therapeutic hypothermia was offered while rest were included as a control group and monitored likewise for the overall survival and neurological outcome. These babies were followed up till 1 month and 3 months of age to assess neurological outcome.
Results: In this study, a total of 47 patients were enrolled both from extramural and intramural NICU set ups. Of them, 22 patients were offered Therapeutic Hypothermia and 25 patients were given standard post asphyxia care. 7 out of 9 inborn patients and 3 out of 13 out born neonates who were offered therapeutic hypothermia survived whereas 5 out of 11 inborn and 4 out of 14 out born neonates who were offered standard post asphyxia care survived.
Conclusions: Therapeutic hypothermia cannot be attributed to significant increase or decrease in mortality when compared with standard care group. No inference could be made about hypothermic neuroprotection in the follow up study. Overall survival outcome was better in inborn patients than that of outborn. Inborn neonates subjected to therapeutic hypothermia, showed a trend towards better survival than those given standard post asphyxia care.

Keywords: Perinatal asphyxia, Therapeutic hypothermia, CRITICOOL™, Neurodevelopmental disability

INTRODUCTION

Therapeutic hypothermia is neuroprotective by inhibiting several steps in the excito toxic oxidative cascade.[1] 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 in terms of survival, motor palsy and neurodisability.[2] It is to be continued for a period of 72 hours for better neuro protection. Neonatal encephalopathy is the cause of 1 million deaths worldwide every year, of which 99% occur in low-income and middle-income countries (LMICs). Death or disability is reduced at 18 months through use of induced hypothermia for moderate or severe neonatal encephalopathy.[3]

Aim and objectives

Aim and objectives of current study were to examine whether whole body cooling reduces death or moderate to severe neuro-disability in cases of perinatal asphyxia. Secondary objective is to asses neurological status at discharge, 1 month of age and 3 months of age after hypoxic ischemic encephalopathy.

METHODS

Study design, population and location

This is A Prospective Non-Randomized Comparative Study, wherein term neonates with severe birth asphyxia fulfilling the inclusion and exclusion criteria were offered therapeutic hypothermia by means of availability of whole-body cooling device; CRITICOOL™ and were classified as the CASE group and those whom we couldn't offer the cooling device were taken as the CONTROL group. Both these groups were monitored for immediate morbidity due to birth asphyxia and assessed for neurological outcome at discharge. Patients were followed up for 1 month and 3 months of age after neonatal encephalopathy and assessed for neurological outcome and neuro-disability. Term Newborns with severe perinatal asphyxia admitted in intramural and extramural NICU at department of paediatrics, SSG hospital, Vadodara who were fulfilling the inclusion and exclusion criteria were enrolled in the study.

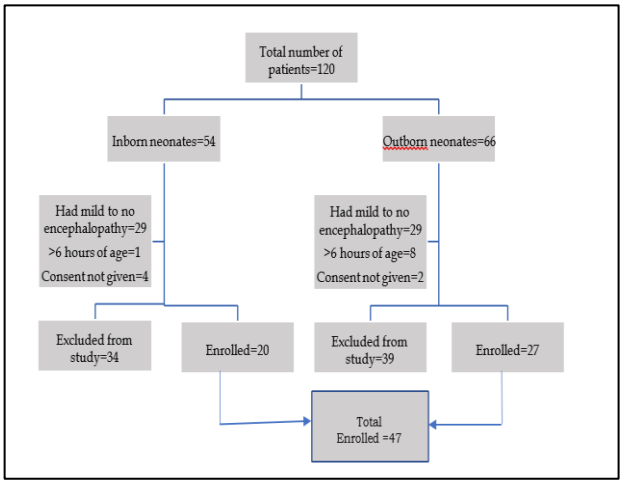

Figure 1: Screening and selection of studies.

Sample size

A time bound study over a period of 10 months was carried out. Varying upon accessibility of automated device CRITICOOL at a given time for patients with neonatal asphyxia in accordance with inclusion criteria, case and control groups were designed. 22 Patients fulfilling the inclusion and exclusion criteria were offered therapeutic hypothermia. Rest 25 term neonates with severe birth asphyxia who couldn't avail the cooling device or did not give consent were taken as the Control group and were monitored and assessed for neurological outcome.

Inclusion criteria

Inclusion criteria were; post menstrual age ≥36 weeks, birth weight ≥2 kg, Age ≤6 hours, evidence of fetal distress or neonatal asphyxia from either of the following: h/o acute perinatal event (placental abruption, cord prolapse, severe FHR abnormality) or pH ≤7.0 or 5 min APGAR ≤6 or lack of crying by 5 minutes of age in home delivery or assisted ventilation initiated at birth and continued for at least 10 min, evidence of moderate to severe neonatal encephalopathy.

Exclusion criteria

Exclusion criteria were; *p*resence of lethal chromosomal abnormality, presence of severe congenital anomalies, significant bleeding diathesis and major intracranial haemorrhage.

Procedure

Therapeutic hypothermia was administered using a servo-controlled whole-body cooling device, CRITICOOL It maintained rectal temperature of the baby within 33.5 C. After 72 hours of cooling, baby was automatically rewarmed at 0.5 C per hour by the cooling device, CRITICOOL to reach the target temperature of 36.5 C within 6 to 8 hours. The study was carried out from March 2022 to December 2022. The results were statistically analysed using MedCalc, Social Science Statistics Calculator and Microsoft Excel software.[4,5]

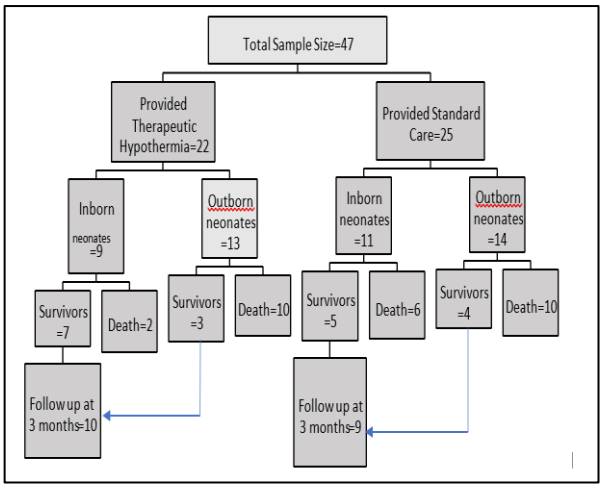

Figure 2: Trial profile.

RESULTS

Out of the 120 participants, over a period of 10 months study,20 inborn neonates and 27 outborn neonates were

taken ahead for the study as illustrated in (Figure 1). From them, as shown in (Figure 2), the participants, Cases were subjected to therapeutic hypothermia and standard post asphyxia care as control study and survival outcome was studied.

Table 1: Maternal characteristics.

Parameters	Therapeutic hypothermia group (n=22)	Standard care group (n=25)
	N (%)	N (%)
Maternal characteristics		
Age, mean (SD) (years)	24.7 (3.85)	25.3 (3.41)
Gravida, median (IQR)	2 (0-4)	2 (0-4)
Parity, median (IQR)	2 (0-4)	2 (0-4)
Pregnancy complications		
Hypertension or preeclampsia	1 (4.54)	0
Antepartum haemorrhage	0	0
Thyroid dysfunction	1 (4.54)	1 (4)
Diabetes	0	0
Intrapartum complications		
Cord mishap (prolapse, rupture)	1 (4.54)	0
Vaginal delivered	19 (86)	22 (88)
Emergency caesarean delivery	3 (13.6)	3 (12)

IQR-interquartile range.

No bias has taken place while choosing subjects for the standard care groups. The hospital has only one machine for administering therapeutic hypothermia, and a single patient occupies the machine for as much as four days. Thus, patients who could not be provided therapeutic hypothermia or in whom consent was refrained were given standard post asphyxia neonatal care immediately and routine blood investigations were sent as per standard protocol and they were given full access to ventilation and inotropic support and intensive monitoring was continued.

Analysing the maternal parameters of pregnancy, labour and related complications for the study, as were comparable, depicted in Table no. 1, both the therapeutic hypothermic and standard care group exhibit similar values in almost all parameters. All the mothers had taken Antenatal Care considering minimum 3 antenatal visits to health care facility.

8 instances of cardiac arrythmias were noted in the therapeutic hypothermic group (36.3%) while the standard care group did not present with any cases of arrythmias. Arrhythmias noted were in form of Bradycardia with heart rate reaching 85-100/ minute, encountered in about 8 patients at around 40-60 hours of cooling. The lowest recorded Heart Rate was 89/min with an earliest manifestation at 43 hours of cooling. Analysis using Fischer's exact test showed that this particular result showed a significant result in favour of the standard care group.

Table 2: Neonatal characteristics.

Parameters	Therapeutic hypothermia group (n=22)	Standard care group (n=25)
Neonatal characteristics		
Male sex, N (%)	14 (63.6%)	14 (56%)
Gestational age (weeks), mean (SD)	38 (1.13)	38 (1.19)
Birth weight (gm) mean (SD)	2600 (344.3)	2538.2 (365.3)
Head circumference (cm) mean (SD)	33.07 (1.20)	33.04 (1.15)
Extent of resuscitation, N (%)		
IPPV with bag & mask	11 (50)	13 (52)
IPPV with bag & tube	10 (45.45)	10 (40)
Chest compressions	1 (4.54)	2 (8)
Medications	0	0
APGAR score (median, Q1-Q3, % <5)		
1 min after birth	3	2
5 min after birth	5	4
10 min after birth	7	6
Arterial blood gas, mean (SD)		
pH (first available)	7.03 (0.182)	6.96 (0.275)
Base deficit (mEq/l)	-13.60 (9.35)	-17.50 (6.398)
Encephalopathy, N (%)		
Moderate encephalopathy	12 (54.5)	14 (56)
Severe encephalopathy	10 (45.45)	11 (44)
Clinical seizures, N (%)	9 (40.90)	9 (36)
Refractory seizures, N (%)	0	1 (4)
Inotropic support, N (%)	14 (63.6)	18 (72)
Ventilatory requirement, N (%)	22 (100)	25 (100)

[a]Chi square test for testing equality of proportions, Fisher exact test when n<5, Two-sample t-test for means. Analysing the neonatal parameters, there was no significant difference in neonatal factors studied amongst participants in both groups.

Similarly, many other studies have documented bradyarrhythmias as a complication of therapeutic hypothermia.[6] There were no fluctuations in hemodynamic stability of neonates and hence none required aborting the cooling procedure within 72 hours. Although a pattern has started to emerge wherein the percentage of patients receiving therapeutic hypothermia is higher, it is wise to remember that except Cardiac Arrhythmias, none of these observations were found to be

statistically significant, and no difference between higher mortality in cooling and standard care group could be established. Although, the sample size enrolled in our study is small, hence an association between therapeutic hypothermia administration and better prognosis or worsening cannot be established and its impact cannot be commented.

Tests for laboratory parameters

The pH value taken was from the first available arterial pH on receiving the neonate. Improvement of pH was considered comparing the first receiving pH and change in pH after 24 hours of post asphyxia care. With this study we could concluded that both the modes, therapeutic hypothermia and standard post asphyxia care were successful in improving the pH of asphyxiated newborns.

Table 3: Neonatal morbidities post asphyxia.

Adverse events	N (%)		P value
	Therapeutic hypothermia group (n=22)	Standard care group (n=25)	
Meconium-stained liquor	13 (59.09)	12 (48)	0.45
Meconium aspiration syndrome	6 (27)	5 (20)	0.57
Complications observed in post asphyxia period (within 72 hrs)			
Arrhythmias	8 (36.36)	0	0.004
Persistent metabolic acidosis (>24 hrs)	2 (9.09)	4 (16)	0.78
Dic (lab parameter)	4 (18.18)	7 (28.0)	0.65
Thrombocytopenia	5 (22.7)	3 (12.0)	0.55
Altered skin integrity	0	0	-
Pulmonary haemorrhage	0	0	-
Pneumothorax	1 (4.5)	0	0.46
Persistent gastrointestinal bleed	1(4.5)	2 (8)	0.90
Sclerema	3 (13.6)	6 (24)	0.47
Subcutaneous fat necrosis	0	0	-
Shock	16 (72.7)	20 (80)	0.73
Persistent pulmonary arterial hypertension	11 (50)	11 (44)	0.65
Culture proven sepsis	2 (9.09)	2 (8)	0.69
Complications observed in post asphyxia period (within 72 hrs)			
Shock	2 (9.09)	3 (12)	0.87
Multi-organ dysfunction (MODS)	3 (13.6)	4 (16)	0.85
Clinical seizures (any time)	9 (40.90)	9 (36)	0.96
EEG recording done	10 (45.4)	12 (48)	-
Abnormal EEG background	7 (31.81)	10 (40)	0.81

Table 4: Prognostic markers.

Parameters	Therapeutic hypothermia group (N=22), Frequency (%)
Abnormalities in USG cranium	3 (13.6)
Abnormal EEG findings	
Epileptiform activity present	3 (13.6)
If yes, then number present in frontal region	2 (9.09)
Abnormalities in MRI findings	2 (9.09)
Defective/absent myelination	1 (4.5)
Early feeding initiated (within 3 days)	6 (27.2)
Feeding tube omitted before 7 days	7 (31.8)

Table 5: Outcomes.

Parameters	Therapeutic hypothermia group (n=22),	Standard care group (n=25),
	N (%)	N (%)
Discharge	10 (45.4)	9 (36)
DAMA	0	1 (4)
Death	12 (54.5)	15 (60)

Tests for objective markers for prediction of survival

Both the therapeutic hypothermia (13.6%) and standard care group presented with 3 cases of USG cranium abnormalities (12%) each. 1 patient each in therapeutic hypothermic and standard care group showed finding of multiple subependymal cyst. Along similar lines, 1 patient each from the therapeutic hypothermia and standard care group showed presence of GMH-1 and 1 patient each presented with raised cortical echogenicity in the bilateral periventricular region. However, findings were not characteristic of HIE.

Table 6: Follow-up outcomes of survivors (after 3 months).

Parameters	Therapeutic hypothermia group (N=10), Frequency (%)	Standard care group (N=12), Frequency (%)	P value
Normal head growth	7 (70)	7 (58.3)	0.9
Severe motor disability	0	2 (16.6)	0.49
Requirement of antiepileptic drugs	6 (60)	8 (66.6)	0.9
Not attained exclusive breast feeding until discharge	1 (10)	3 (25)	0.72
Hearing impairment	2 (20)	3 (25)	0.81
Visual impairment	1 (10)	3 (25)	0.72

Table 7: Overall Survival rates in relation to the place of delivery (inborn/outborn).

Parameters	Death, N (%)	Survivors, N (%)	Total
Outborn	20 (74)	7 (25)	27
Inborn	8 (40)	12 (60)	20
Total	28 (59.5)	19 (40)	47

The Chi-square statistic is 5.539. The p value is 0.018598. Significant at $p<0.05$. The Chi-square statistic with Yates correction is 4.2145. The p value is 0.040081. Significant at $p<0.05$.

Table 8: Survival rates among different mode of post asphyxia care groups differ in Inborn and Outborn patients.

Parameters		Death, N (%)	Survivors, N (%)	Total
Inborn	Therapeutic hypothermia group	2 (22)	7 (77)	9
	Standard care group	6 (54)	5 (45)	11
Outborn	Therapeutic hypothermia group	10 (76)	3 (23)	13
	Standard care group	10 (71)	4 (28)	14

Similarly, 3 patients from both the therapeutic hypothermic and standard care group had abnormal epileptiform activity upon conducting EEG. 2 out of the 3 cases in each group had epileptiform activity in the frontal region, while the remaining one had activity in the occipital region of the brain. EEG of a patient was done only after completion of the rewarming procedure.

MRI abnormalities were seen in 2 cases each of therapeutic hypothermia (9.09%) and standard care groups (8%), out of which 1 therapeutic hypothermic in both groups were of absent or defective myelination. MRI was only performed after the patient had achieved haemodynamic stability. 1.5 Tesla MRI Scans were conducted which was possible with our institutional facility.

Early feeding was initiated in 6 patients of the therapeutic hypothermic group (27.2%) and 5 patients in the standard care group (20%). Tube feeding was omitted within 7 days in 7 patients of the therapeutic hypothermic group (31.8%) and 9 patients of the standard care group (36%). None of these findings showed any statistical significance.

Checking for death as the primary outcome

Risk ratio=(12/22)/(15/25)=0.90, The risk of poor outcome in neonates treated with therapeutic hypothermia is 0.90 times the risk of poor outcome in patients treated with conventional therapy. However, with 95% CI cutoffs ranging from 0.5525 to 1.4958, the finding is rendered statistically Not significant, since the above range also includes the null value 1.0. To check for significance, Chi square test has been employed: The Chi-square statistic along with Yates correction is 0.0067. The p value is 0.934831. The trial failed to show any significant association between usage of therapeutic hypothermia and increase in survivability of the neonate.

The patients who survived were called for a routine check-up at 3 months. All survivors were present and

hence no loss was noted. 7 patients in both the therapeutic hypothermic (70%) and standard care group (58.3%) had normal head growth. The three patients of the therapeutic cooling group showed decreased rate of adequate increase in head size (about 0.5cm per week). In the standard care group ,5 of the patients with abnormal head growth showed receding forehead with early fusion of suture lines in 2 of them. The other 3 had inadequate growth of Head Size (i.e., less than 0.5cm per week) of about 3 cm in 3 months counting it to be the half of the desired. Nobody presented with hydrocephalus. 2 patients in the standard care group (16.6%) presented with severe motor disability. This was not seen in the therapeutic hypothermic group. 6 patients from the therapeutic hypothermic group (60%) and 8 patients from the standard care group (66.6%) required antiepileptic drugs and required single antiepileptic, Levetiracetam which was used in our set up. However, there was one patient noted with Refractory Seizures that required 4 antiepileptics (phenobarbitone, phenytoin, levetiracetam and clonazepam) belonging to standard care group in view of refractory seizures who eventually took DAMA on oral antiepileptic drugs. Feeding difficulties were present in 1 patient from the therapeutic hypothermic group (10%) and 3 patients from the standard care group (25%) in form of inability to exclusively breast feed and were discharged on Katori Pallad feeding. However, 1 patient from the standard care group, a case with refractory seizures took DAMA on tube feeding. Hearing impairment was

also noticed using OAE test (BERA test pending). It occurred in 2 patients from the therapeutic hypothermic group (20%) and 3 patients from the standard care group (25%). 1 patient from the therapeutic hypothermic group (10%) and 3 patients from the standard care group (25%) had impairment of vision. Cause of visual impairment of the patient in the therapeutic hypothermic group was squint, while in the standard care group, 1 patient presented with squint and 2 with nystagmus. Visual evoked potential testing could not perform and hence cortical visual impairment could be documented. It is important to note that none of the above findings were found to be statistically significant at a 95% confidence interval. However, it is not enough to just compare cases of patients put on therapeutic hypothermia therapy with patients put on standard care. We must also compare patients born inside the hospital with patients born outside the hospital to properly visualize the benefits of early initiation of therapeutic hypothermia.

A significant association has been established between survival and inborn neonates irrespective of mode of the post asphyxia treatment offered. The null hypothesis is rejected. This is important since it demonstrates that therapeutic hypothermia in inborn neonates is linked to increased chances of survivability. Patients born outside the hospital in peripheral health centres do not receive early access to post asphyxia resuscitation and stabilization and early standard transport facilities and had decreased availability of inotropes at birth. We could initiate therapeutic hypothermia at an average of 4 hours of life within a minimum of 1hour of age to 5 hours of age to if patient arrived at our set up well in time and hence therapeutic hypothermia benefitted to prevent secondary energy failure in asphyxia.

For survival rate of inborn neonates, The Chi-square statistic is 2.1549. The p value is 0.142117. Not significant at $p<0.05$. The Chi-square statistic with Yates correction is 1.0185. The p value is 0.312871. Not significant at $p<0.05$. Hence there is no significant association of survival outcome in Inborn patients with modes of post asphyxia care provided. Inborn babies receive immediate standardized resuscitation (as per NRP) and post asphyxia neonatal care is available immediately in the hospital, patients receiving standard care and patients receiving therapeutic hypothermia have not shown any significant difference in survivability rates. This is important since it also demonstrates that therapeutic hypothermia in inborn neonates is linked to increased chances of survivability. Patients born outside the hospital in peripheral health centres do not receive early access to post asphyxia resuscitation and stabilization and early standard transport facilities and had decreased availability of inotropes at birth. We could initiate therapeutic hypothermia at an average of 4 hours of life within a minimum of 1hour of age to 5 hours of age to if patient arrived at our set up well in time and hence therapeutic hypothermia benefitted to prevent secondary energy failure in asphyxia. Survival rates from different mode of post asphyxia care in outborn patients (n=27). The Chi-square statistic is 0.106. The p value is 0.744785. Not significant at $p<0.05$. The chi-square statistic with Yates correction is 0.013. The p value is 0.909291. Not significant at $p<0.05$. Hence there is no statistically significant evidence of survival outcomes pertaining to the mode of care given in outborn neonates and percentage mortality between two treatment groups is nearly equal.

DISCUSSION

HIE does not refer to a single event but rather refers to a continuing process beginning from the time of hypoxic insult. There are two different episodes of neuronal impairment which are known to occur during HIE. The immediate hypoxic insult is called the primary phase and this is followed by a short period of recovery (latent phase) lasting for approximately six hours. Subsequently there is a longer phase during which there is a release of chemical mediators causing secondary neuronal damage.[7] Neurons may die during the actual ischemic or primary phase itself. Several neurons however recover at least partially in the 'latent' phase but die hours or even days later (secondary or delayed cell death). An “excito toxic-oxidative cascade” characterized by excessive stimulation of neurotransmitter receptors and membrane depolarization causing increased intracellular calcium is also observed. Increased levels of intracellular calcium

activate nitric oxide synthase to perpetuate the release of nitric oxide, which in turn affects mitochondrial respiration.[1] Therapeutic hypothermia is neuroprotective by inhibiting several steps in the excito toxic 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 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 favorably affect outcome in newborn and adult animals.[8]

TH and has become the standard of care for HIE in developed countries. However, in underdeveloped and transitional countries where the problem is more common, therapeutic cooling is still in the nascent phase. There are several reasons for this in resource restricted settings. Similarly, despite availability of compelling clinical evidence that TH initiated within a few hours after hypoxic insult can improve neurological outcome in term infants, implementing the same in resource restricted settings of India is not that easy mainly because of the non-availability of expensive devices used for providing TH in developed countries. Recently, two systematic reviews on the efficacy and safety of TH in low- and middle-income resource settings have been published. The systematic review by Pauliah et al did not find any statistically significant reduction in neonatal mortality in underdeveloped countries although the confidence intervals were wide. Galvao et al observed that there is ample evidence for designating hypothermia as the standard of care for HIE but more evidence from low-income countries is required.[9] Our study, being carried at an Indian tertiary care centre is a small representative to the subset of cooling in low- and middle-income countries.

In this study, a total of 47 patients were enrolled both from extramural and intramural NICU set ups. Of them, 22 patients were offered therapeutic hypothermia and 25 patients were given standard post asphyxia care. Both maternal and neonatal characteristics were comparable amongst neonates of both the groups. Post asphyxia management was statistically significant to improve arterial pH and lactic acidosis of asphyxiated neonates. However, there was no statistically significant difference between the mode of treatment availed. There was major incidence of cardiac arrhythmias in form of bradycardia in 8 patients (36%) of the 22 patients provided with therapeutic hypothermia which turned out to be statistically significant complications during cooling, however, none required pharmacological intervention for the same. There was 54.5% mortality (12/22) in the group provided therapeutic hypothermia and 60% mortality (15/22) in that of standard care group. However, it turned out to be statistically not significant. However, there was significant difference between overall survival outcome of Inborn Patients 12 out of 22 (60%) when compared to the Outborn Patients, 7 out of 27 (25%) which proved to be statistically significant. Also, the inborn neonates when subjected to therapeutic hypothermia showed better survival outcome, 7 out of 9 (77.77%) than their outborn counterparts, 3 out of 13 (23%) being statistically significant. During the procedure of therapeutic hypothermia, no patient required abortion of cooling process in due course of 72 hours.

Cooling in low- and middle-income countries

There has been considerable debate regarding the use of cooling in low- and middle-income countries. Increased rates of maternal malnutrition, inadequate maternal pelvis size, poor antenatal obstetric care, late referral of complicated pregnancies, lack of trained birth attendants for and basic equipment for neonatal resuscitation, lack of referral centers that can manage neonates that require ventilation, increased rates of HIV, malaria and puerperal sepsis are factors that increase the risk of perinatal asphyxia. Neonatal encephalopathy is the cause of 1 million deaths worldwide every year, of which 99% occur in low-income and middle-income countries (LMICs). The pooled data from clinical trials in high-income countries suggest that death or disability is reduced at 18 months through use of induced hypothermia for moderate or severe neonatal encephalopathy.[10] Although several trials have suggested that there are beneficial effects of hypothermia in LMICs, these studies have been small or poorly designed, or both, and systematic reviews have reported conflicting results. The international liaison committee resuscitation guidelines in 2015 recommended therapeutic hypothermia as the standard of care in LMICs for neonatal encephalopathy, but acknowledged that the existing evidence was weak. Nevertheless, hypothermia therapy has been extensively implemented in most LMICs as the standard care and adopted into their national guidelines.[11]

Hypothermia for moderate or severe neonatal encephalopathy in low-income and middle-income countries (HELIX)

HELIX trial was conducted as a multicounty open-label, randomised controlled trial in seven tertiary neonatal intensive care units in India, Sri Lanka, and Bangladesh. They enrolled infants born at or after 36 weeks of gestation with moderate or severe neonatal encephalopathy and a need for continued resuscitation at 5 min of age or an Apgar score of less than 6 at 5 min of age (for babies born in a hospital), or both, or an absence of crying by 5 min of age (for babies born at home).

Using a web-based randomisation system, they allocated infants into a group receiving whole body hypothermia (33.5°C) for 72 h using a servo-controlled cooling device, or to usual care (control group), within 6 h of birth. All recruiting sites had facilities for invasive ventilation, cardiovascular support, and access to 3 Tesla MRI scanners and spectroscopy. It was examined whether therapeutic hypothermia that is initiated within 6 hours of birth and continued for 72 hours reduces death or disability at 18–22 months when compared with usual care, in full-term babies with moderate or severe neonatal encephalopathy who have been admitted to tertiary neonatal units in LMICs.[11] In the study, of the 2296 infants screened for eligibility between Aug 15, 2015, and Feb 15, 2019, 576 infants were considered eligible for inclusion and 1720 infants were excluded as per exclusion criteria. After 168 exclusions, 408 were randomly assigned to groups at the seven hospitals in India (N=347), Bangladesh (N=33), and Sri Lanka (N=28). 202 infants were allocated to the hypothermia group and 206 infants were allocated to the control group. The neurodevelopmental paediatricians did the neurological examinations between Jan 6, 2017, and Sept 27, 2020, when the infants were aged 18-22 months. The trial then concluded that Therapeutic hypothermia did not reduce the combined outcome of death or disability at 18 months after neonatal encephalopathy in low-income and middle-income countries, but significantly increased death alone. Therapeutic hypothermia should not be offered as treatment for neonatal encephalopathy in low-income and middle-income countries, even when tertiary neonatal intensive care facilities are available.[11]

Description of other studies conducted

Various trials have been reviewed for therapeutic hypothermia carried out in Cochrane meta-analysis. HELIX Trial is the only trial that was conducted in Low Income Countries.[6,11] By far very few trials have been conducted in Indian Setup namely Helix Trial, Bharadwaj et al, Bhat et al; whereas western countries and developing nations have larger number of studies.[12,14]

Also, Therapeutic Hypothermia is accepted as standard of care in western set up.[11] Eleven randomized controlled trials met inclusion criteria for this review, including eight previously identified.[11] All these trials had been conducted at different centres while using different cooling materials. (Gunn 1998; Akisu 2003; Cool Cap Study 2005; Eicher 2005; NICHD Study 2005; Lin 2006; ICE Study 2011; Shankaran 2002) and three new studies (TOBY Study 2009; neo.nEURO Study 2010; Zhou 2010). Two studies (NICHD Study 2005; ICE Study 2011) had additional data reported, which is included in this analysis. Five were performed as pilot studies, two in single centres Turkey (Akisu 2003) and China (Lin 2006)), two at multiple centres in North America (Shankaran 2002; Eicher 2005) and one in New Zealand (Gunn 1998). Six large multicentre randomised controlled trials have been published, one from the National Institute of Child Health and Human Development (NICHD) network in North America (NICHD Study 2005), one from multiple centres in China (Zhou 2010) and four from multiple international centres (Cool Cap Study 2005; TOBY Study 2009; neo.nEURO Study 2010; ICE Study 2011).[7]

Need for follow up

The Cochrane meta-analysis of 11 RCTs on TH has shown significant reduction in the composite outcome of mortality or major neurodevelopmental disability at 18 months of age.[6] Though Therapeutic hypothermia significantly reduces neuro-morbidity as compared to standard care, yet among the surviving infants a sizeable number suffer from varying degrees of neuro-disability, which emphasizes the need for rigorous long-term follow-up of these children. Shankaran et al have published outcomes following Therapeutic hypothermia at 6-7 years of age, in which though it did not result in significant reduction in the combined outcome of death or an IQ score below 70 at 6 to 7 years of age, it was still shown to reduce the rate of death with no increase in the rates of a low IQ score or severe disability among survivors.[11] In our study being time bound for a period of over 10 months, we performed neuro-disability assessment at 3 months of age.

Follow up during NICU stay

Findings of a structured neuro exam needs to be documented daily during and at least until 1 week after therapeutic hypothermia.[13] Though it is often not possible to perform a complete examination due to the infant's sickness, intubation and effect of sedatives and anti-seizure medications. Sarnat staging and Thompson scoring are two such examination methods. Levene's classification is a simplified system, shorter and easy to perform. Though significant correlation exists between developmental status at 2 years and the Sarnat grade and persistently abnormal neuro exam on day 3, the best predictability of the outcome at 2 years is seen with the neurological examination at discharge.

Frequency of follow up

The first visit may be planned at 2 weeks post discharge. Thereafter at 3, 6, 9, 12, 18 and 24 months or 2, 4, 8-, 12-, 18- and 24-months corrected age. As the child needs to come at 6, 10 and 14 weeks for immunization, the initial few visits may be combined with these. Then on, every 6 monthly or yearly till follow-up lasts.[13]The 18-24 months visit is mandatory for formal development assessment. In case the child develops any medical or neurodevelopmental concerns, more frequent visits will be required. Our study being time bound for a period of over 10 months, we performed neuro-disability assessment at 3 months of age.

Limitations

This study was an equipment dependent study and due to availability of single cooling device, CRITICOOL™, that occupied a single patient for about four days, we could not enrol optimum number of eligible patients for cooling and those patients who were eligible and couldn't avail the machine were given standard care of post-asphyxia treatment, making this study non- randomized. This being a time bound study carried over a span of 10 months, a smaller sample size could be enrolled which lead to statistical fallacies for significant conclusions. We did not have availability of continuous aEEG monitoring. Hence, response to therapeutic hypothermia in seizures arising as a result of early onset of fetal brain injury could not be serially monitored. Being a time bound study over a 10-month period, outcome of therapeutic hypothermia in terms of decrease in severe neuro-disabilities couldn't be evaluated as they have not been followed up until 18 to 22 months of age of the infants.

CONCLUSION

From our current study, therapeutic hypothermia could not be attributed to significantly increase or decrease mortality when compared with standard care group. Post asphyxia complications pertaining to cardiac arrhythmias in form of bradycardia were characteristically found associated with therapeutic hypothermia which turned out to be statistically significant. Therapeutic hypothermia has not proved to attribute to either increase or decrease in overall survival outcome of asphyxiated neonates. Overall survival outcome was more in inborn patients than that in outborn patients. Therapeutic hypothermia when offered in inborn patients, has reported to have increased survival outcome than that given in the outborn neonates. Inborn neonates when subjected to therapeutic hypothermia, showed a trend towards better survival than those given standard post asphyxia care.

Recommendations

Larger multicentric trials with Inborn neonates should be taken for us to evaluate increased survival rates and further follow up to assess neurodevelopmental outcomes at 18 to 22 months of age. Availability of trained medical personnel for immediate post resuscitative and stabilization care and early neonatal transport facilities would aid in better neonatal outcomes in post asphyxia management for Outborn neonates. It is imperative that NICUs offering Therapeutic Hypothermia have good quality NICU Care reflected in their risk adjusted outcomes. The facilities must have access to bedside ultrasonography, EEG, Magnetic Resonance Imaging and 2D echocardiography. The units must be capable of providing life support, continuous physiologic monitoring and access to multidisciplinary team for managing neonates both during acute stay in the NICU and during Follow up for at least 18 months. Therapeutic Hypothermia shouldn't be tried at centres with no infrastructural facilities available and where stringent post asphyxia vital monitoring couldn't be carried out.

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