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Original Article

Clinical Profile, Mortality, and Short-term Outcome in Asphyxiated Neonates Receiving Therapeutic Hypothermia in a Limited Resource Setting: A Cohort Study

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ABSTRACT

Background: This study aimed to evaluate the effectiveness of therapeutic hypothermia (TH) among asphyxiated newborns for reducing mortality, adverse clinical events, and short-term outcomes in comparison to asphyxiated newborns not receiving TH.

Methods: This non-randomized cohort study was conducted at a tertiary care center. The statistical population of the study consisted of asphyxiated newborns admitted in the neonatal intensive care unit within 24 h of life meeting the laboratory and/or clinical criteria of severe birth asphyxia. Eligible newborns, who received TH, were labeled as recipients and those who did not receive TH were labeled as non-recipients.

Results: Out of 176 studied neonates, 89 cases received TH, while 87 of the subjects did not receive TH. The recipients of TH had a 15.3% lower mortality rate, compared to non-recipients (P<0.05). The incidence of adverse clinical events was similar among both groups. At the time of discharge, 73.2% and 56.8%, 92.6% and 70.1%, 30.4% and 46.2% of recipients and non-recipients were neurologically normal (P=0.01), able to breastfeed (P<0.05), and required anti-epileptics (P<0.05), respectively.

Conclusion It can be concluded that TH was an effective and feasible therapy with decreased death rate, better neurological status at discharge, and lesser need for anti-epileptics without increasing adverse clinical events at limited-resource settings using low-cost devices.

Keywords: Adverse clinical events, Limited resource settings, Neonatal mortality, Neurological outcome, Therapeutic hypothermia

Introduction

Perinatal asphyxia is a major cause of perinatal mortality in India. In developed countries, the incidence of perinatal asphyxia is estimated at 1-8 per 1,000 live births; however, this rate is higher in developing countries reaching 26 per 1,000 live births (1). Neonatal hypoxic-ischemic encephalopathy (HIE) is a devastating disease that primarily causes neuronal and white matter injury and is caused by perinatal asphyxia. The incidence of HIE is calculated at 1.4% among institutional deliveries, and perinatal asphyxia is found to be responsible for 28.8% of neonatal deaths according to the National Neonatal Perinatal Database report (2). Hypoxic-ischemic encephalopathy has tremendous detrimental effects on the developing brain and is the leading cause of death among neonates. Approximately 25%-60% of survivors are left with permanent neuro-disabilities, such as cerebral palsy, decreased intelligence quotient, cognitive impairment, and seizure disorder (3, 4). These poor outcomes are associated with the lack of any neuroprotective therapy following perinatal asphyxia, in which only supportive treatment is provided.

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The efficacy of therapeutic hypothermia (TH) is well documented in developed countries, and whole-body cooling is now widely being used as the standard therapy in HIE newborns. American Academy of Pediatrics Committee on fetus and newborn also recommended that TH should be started within 6 h of birth and continued for 72 h followed by gradual rewarming in asphyxiated newborns (5). Based on the results of a recent Cochrane review, TH led to a significant reduction in the combined outcome of death or neurodevelopmental disability among asphyxiated newborns at 18 months of age (6). However, safety and efficacy of data on hypothermia therapy from developed countries cooling trials using high-cost cooling devices cannot be applied to developing countries, because of the population demographic differences, co-morbidities, anemia, perinatal infection, growth restriction, meconium aspiration syndrome (MAS), and limited intensive medical care facilities (7). There are insufficient studies to validate its feasibility and efficacy in a limited-resource setting. Nevertheless, the findings of a recent meta-analysis of available studies performed in limited-resource settings (8) and some other studies (9-12) using low-cost cooling devices have shown a decreasing trend towards mortality with the improved neurological outcome without increasing adverse effects in recipients of TH.

As a tertiary care center, this research dealt with a large number of newborns with perinatal asphyxia and its complications, such as high mortality and developmental disabilities. Based on the evidence supported by a meta-analysis of studies at limited-resource settings and the recommendation of Cochrane review regarding the safety and efficacy of TH, a low-cost cooling device was used in our study (6, 8). This study aimed to assess the feasibility and effectiveness of TH protocol by assessing the outcome of asphyxiated newborns regarding survival and short-term neonatal outcome in a limited-resource setting. To the best of our knowledge, the present study was the first to investigate early neurological outcomes using Hammersmith Neonatal Neurological Examination (HNNE) scale and short-term outcomes in the HIE newborns treated with TH in central India.

Methods

This non-randomized prospective cohort study was conducted in the neonatal intensive care unit (NICU) of a tertiary teaching institute. The statistical population consisted of asphyxiated newborns fulfilling the lab and/or clinical criteria of severe birth asphyxia with moderate to severe encephalopathy. Nevertheless, the newborns with < 36 weeks age, < 2,000 gm weight, hypotension (non-invasive blood pressure of <40 mm Hg) requiring adrenaline, persistent hypoxemia (SpO_2<90/PaO_2<50-70 at FiO_2>60% with maximal ventilation support) on admission, and major congenital anomaly were excluded from the study (13, 14). Eligible asphyxiated newborns aged < 6 h received TH (recipients) and those admitted with the age range of 6-24 h were given the standard supportive care (non-recipients) (Figure1). The eligibility criteria for receiving TH were newborns: having ≥ 36 weeks of gestational age; > 2,000 g weight, persistent low Apgar of ≤ 5 at 5 minutes or longer, and/or Acidosis (Cord PH of <7.1 and/or arterial PH of <7.1 or base deficit of 12 or more within 60 min of birth), and/or resuscitation/ventilation at 10 min after birth; and/or evidence of moderate to severe encephalopathy according to modified Sarnat Criteria (13, 14).

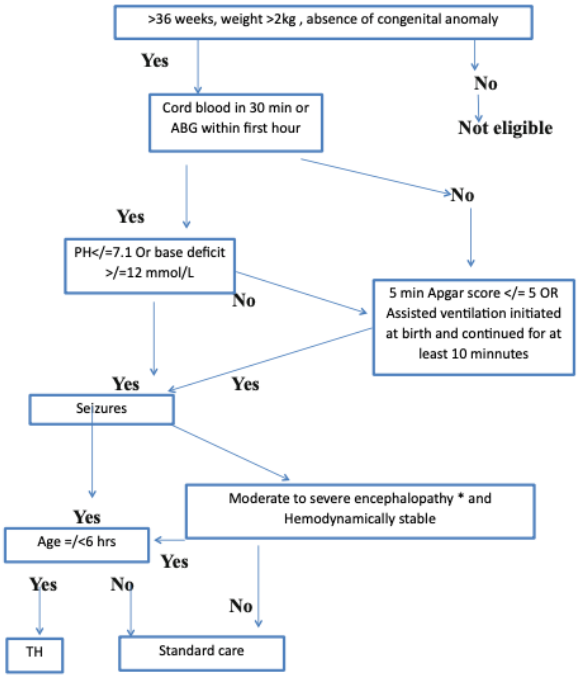

Figure 1. Protocol for Therapeutic Hypothermia

This study was carried out after obtaining approval from an institutional ethics committee of Mahatma Gandhi Memorial Medical College, Indore, India. The baseline demographic information and neonatal data were recorded in a predesigned proforma. Therapeutic hypothermia was administered

using a low-cost cooling device based on phase-changing material (Mira Cradle Neonate Cooler. Mfg. Plus Advanced Technologies Pvt. Ltd India) after taking informed consent from the parents of eligible newborns. The intervention was started within 6 h of birth and maintained for a period of 72 h. A rectal temperature of 33.5±0.5°C was maintained using rectal probes for continuous monitoring of the core temperature. The radiant warmer was switched on if the newborn's recorded core temperature was lower than 33.2°C. After the cooling phase, neonates were slowly rewarmed over 10-12 h (0.5°C/h). Asphyxiated newborns admitted after 6 h of life were placed under radiant warmers in servo-controlled mode and a rectal temperature of 36.5°C was maintained and they were managed as per the standard NICU protocol for HIE (9, 11).

Sarnat and Sarnat staging

In the present study, the researchers monitored the study cohort serially for clinical events, including coagulopathy, bleeding, shock, acute kidney injury, metabolic/electrolyte abnormality, arrhythmias, and skin changes. The neonates in both groups were managed similarly, except receiving TH, and given supportive care, including anticonvulsant medications, inotropic support, and mechanical ventilation when indicated clinically. Early outcomes, including mortality, adverse clinical events, neurological abnormalities, feeding, seizures, need for anti-epileptics, and hospitalization length, were evaluated till discharge. Neurological evaluation was performed using HNNE at the time of discharge from the hospital. The HNNE Scale is a 34-item evaluation scale that takes approximately 10-15 min to administer has been used extensively for neurobehavioral assessment of term and preterm infants. It is valid and reliable for the early prediction of CP among high-risk newborns. Although it is used as a tool for neurological evaluation, it includes an assessment of the newborn's neuro-behavior, in addition to neonatal reflexes, movement, tone, tone patterns, and abnormal neurological signs. Scores range from 0 to 34, with scores below 31 are considered as 'sub-optimal', and neonates with suboptimal scores were recorded as neurologically abnormal in the present study (15, 16).

Statistical Analysis

Data was collected and compiled in the Microsoft Excel software for the master chart. Data analysis was done using SPSS software. The continuous parameters were expressed as mean with standard deviation and the distribution of categorical data as percentages. Chi-square as the test of significance and P-value was calculated wherever required, Unpaired t-tests were used for continuous variables and chi-square tests for categorical variables. P-Values<0.05 were considered significant. The risk was assessed by calculating the relative risk with a 95% confidence interval (CI).

Results

Baseline characters and demographic data were similar among recipients and non- recipients (P>0.05) (Table 1).

Table 1. Baseline maternal and neonatal characteristics

		Recipients . n (%)	Non-recipient. n (%)	P-value
Maternal age (years)	20-24	20 (22.4)	23 (26.4)	0.315
	25-29	41 (46.06)	45 (51.7)	
	30-35	22 (24.71)	17 (19.5)	
	>35	6 (6.74)	2 (2.29)	
Gender	Female	26 (30.3)	37 (42.5)	0.450
	Male	63 (69.3)	50 (57.4)	
Birth weight	<2.5 kg	25 (28.08)	35 (40.2)	0.08
	>2.5 kg	64 (71.91)	52 (59.77)	
Gestational age (weeks)	>37	74 (83.1)	73 (83.9)	0.89
	<37	15 (16.85)	14 (16.09)	
Mode of delivery	LSCS	29 (32.5)	33 (37.9)	0.457
	NVD	60 (67.41)	54 (62.06)	
HIE grading	Stage 2	71 (79.7)	59 (67.81)	0.07
	Stage 3	18 (20.2)	28 (32.1)	
MSL	Present	21 (23.5)	23 (26.4)	0.396

LSCS: Lower (uterine) segment cesarean section; NVD: Normal vaginal delivery; HIE: Hypoxic-ischemic encephalopathy; MSL: Meconium stained liquor

Table 2. Adverse clinical events of the cohort during the first 72 hours of age

Variable	Recipient. n (%)	Non-recipient. n (%)	P-value	95% CI limit	RR
Death	7 (7.6)	20 (22.9)	0.005	1.05-1.36	1.19
HNNE score of <31 at discharge	22 (26.2)	29 (43.2)	0.01	0.3-0.9	0.58
Anti-epileptics at discharge	25 (30.4)	31 (46.2)	0.04	0.42-0.9	0.65
>1 antiepileptic at discharge	12 (14.6)	18 (26.8)	0.02	0.229-0.791	0.426
Successful breastfeeding	76 (92.6)	47 (70.1)	0.003	1.11-1.56	1.32
Average duration of NICU stay (day)	8.4	9.5	<0.05		

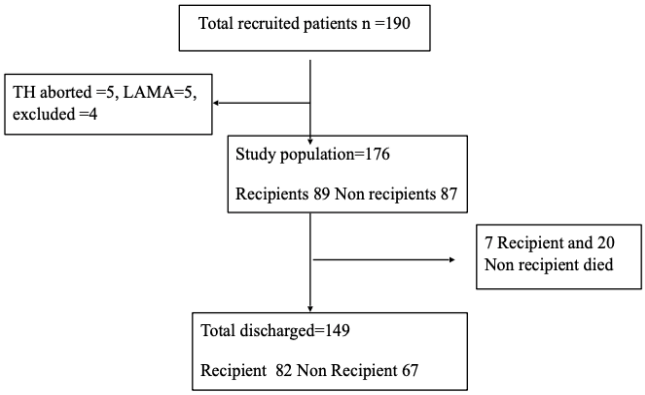

Figure 2. Flow diagram of the participants

Both groups were observed for adverse clinical events during the first 72 h of life, and the participants' clinical profiles were compared during the NICU course. The incidence of metabolic abnormalities, arrhythmias, and coagulopathy was similar in both groups; however, non-recipients recorded a higher incidence of gastrointestinal (GI) bleeding, hypotension, and vasopressor need (Table 2). The occurrences of persistent pulmonary hypertension of the newborn (PPHN), sepsis, acute kidney injury, and severe MAS were also similar among both groups. The searchers of the present study observed that a significantly fewer number of the recipients (5) progressed to severe encephalopathy in comparison to non-recipients (11). The recipients also achieved full enteral feeding earlier at an average of 82 h in comparison to non-recipients (97 h). Fewer number of recipients (41%) required anti-epileptics, compared to non-recipients (56%; P=0.05), and fewer number of recipients (8.9%) required more than 2 anti-epileptics, in comparison to non-recipients (16%; P<0.05) (Table 3).

Among 89 recipients of TH, 7.6% of the cases passed away, while among 87 non-recipients, 22.9% of the subjects passed away during the NICU course. The mortality rate was significantly lower in the recipient group than in the non-recipient group (P<0.05). At the time of discharge, significantly a smaller number of recipients (26.2%) showed a suboptimal score on the HNNE scale in comparison to non-recipients (43%). It was revealed that 30.4% of recipients required anti-epileptics and 14.6% required two or more anti-epileptics at discharge, which was significantly lower in comparison to non-recipients. Moreover, 92.6% of recipients were able to breastfeed successfully, whereas 70.1% of non-recipients were able to breastfeed at discharge. Recipients also had a shorter average duration of stay (8.4 days) in comparison to non-recipients (9.5 days) (Table 4).

Table 3. Clinical profile of study cohort

Variables	Recipient. n (%)	Non-recipient. n (%)	P-value	95% CI	RR
PPHN	8 (8.9)	14 (16.09)	0.154	0.24-1.26	0.55
Moderate to severe MAS	5 (5.61)	9 (10.3)	0.24	0.18-1.5	0.52
Positive sepsis screen	9 (10.11)	11 (12.6)	0.596	0.34-1.83	0.799
Positive blood culture	13 (14.60)	16 (18.3)	0.498	0.40-1.55	0.79
AKI	14 (15.7)	16 (18.3)	0.491	0.19-2.23	0.65
HIE stage progression	5 (7.0)	11 (17)	0.04	0.14-1.04	0.38
Anti-epileptic required	37 (41)	49 (56)	0.05	0.5-1	0.79
2nd Anti-epileptic	18 (21.3)	26 (28.7)	0.68	0.6-1.3	0.9
>2 Anti-epileptics	8 (8.9)	14 (16)	0.02	1.1-2.11	1.5
Full Enteral feeding mean age (hours)	82 (3.4)	97 (4)	<0.05		

PPHN: Persistent pulmonary hypertension of the newborn; MAS: Meconium aspiration syndrome; AKI: Acute kidney injury; HIE: Hypoxic-ischemic encephalopathy

Table 4. Short-term outcome at discharge/death

Variable	Recipient. n (%)	Non-recipient. n (%)	P-value	95% CI limit	RR
Death	7 (7.6)	20 (22.9)	0.005	1.05-1.36	1.19
HNNE score of <31 at discharge	22 (26.2)	29 (43.2)	0.01	0.3-0.9	0.58
Anti-epileptics at discharge	25 (30.4)	31 (46.2)	0.04	0.42-0.9	0.65
>1 antiepileptic at discharge	12 (14.6)	18 (26.8)	0.02	0.229-0.791	0.426
Successful breastfeeding	76 (92.6)	47 (70.1)	0.003	1.11-1.56	1.32
Average duration of NICU stay (day)	8.4	9.5	<0.05		

HNNE: Hammersmith neonatal neurological examination; NICU: Neonatal intensive care unit

Discussion

In developed countries, TH has been studied widely for the last 20 years and is being used as the standard therapy in neonates with perinatal asphyxia (5). The cooling devices used to provide TH, such as tecotherm, cooling blankets, Criticool, and Cool cap, can be high-cost (13). Numerous low-cost devices (e.g., gel packs, fans, water bottles, and phase-change devices) have been used in limited-resource settings to administer TH and have demonstrated their feasibility and efficacy in limited-resource settings (8-12, 17).

Infant cooling evaluation trial, a multi-center randomized controlled trial (RTC) using cooling gel packs to induce TH from Australia, Canada, and New Zealand, showed improved disability-free survival in neonates with moderate to severe HIE after achieving TH with a frozen gel pack (18). The feasibility trial from Christian Medical College, Vellore showed the safety and effectiveness of frozen gel packs for TH (12). Few recent studies also reported a significant improvement in decreasing mortality, morbidity, and neurological abnormality in newborns using low-cost cooling devices based on phase-changing materials (9, 11, 17, 19). The results of the present study using phase-changing material are also consistent with the data of studies using low-cost and high-cost cooling devices.

The best neuroprotection is achieved if cooling is started before 6 h of life when there is still a "therapeutic window", during which secondary re-perfusion injury can be prevented or reduced by providing TH (13, 20, 21). Few studies even recommended cooling before 3 h of age to achieve optimal neuroprotection (19, 21). In a total body hypothermia trial, TH was found to be more effective in newborns receiving treatment in the first 4 h after birth (22). The mean age of starting TH was 3.8±1 h in the present study. Inborn newborns had a shorter mean age of starting therapy (2.5 h) than out-born newborns (4.5 h). The mean rectal temperature was obtained at 35.3°C at the initiation of cooling, and the time taken to reach the target temperature was 85 min. The average temperature during the maintenance phase was estimated at 33.50°C, and 5% of recipients recorded temperature readings outside the target range. Similar observations were reported in a study performed by Thomas et al. (11) using phase changing material, in which the mean age of cooling, mean rectal temperature at initiation, and mean time taken to reach target temperature were 2.9 h, 35.2°C, and 90 min, respectively. In our study, the mean age of starting TH was higher (3.8 h) since the out-born newborns who were reaching the hospital with some delay after birth were also included. In another study conducted by Robert et al. (21), the mean age of cooling was estimated at 1.7 h and the time to reach the target temperature was obtained at 1.9 h owing to better transport and referring facility. Our tertiary care center receives a high number of referrals from peripheral hospitals, and the majority of out-born newborns were referred late due to the lack of knowledge about newer therapy and limited availability of transport facilities contributing to a significant delay in the onset of the cooling. The need to start TH before 6 h of birth is the major limitation of its applicability in limited-resource settings. This issue has been discussed in other studies analyzing the feasibility of TH in low and middle-income countries (8, 12) as the therapeutic window for cooling was already passed due to delayed admission and lack of transport facilities.

During TH therapy, various clinical events in the study cohort were recorded, such as PPHN, severe meconium aspiration syndrome, sepsis, coagulopathy, acute kidney injury, hypoglycaemia, hypocalcaemia, gastrointestinal (GI) bleeding, skin changes, arrhythmias, and hypotension and it was observed that TH did not increase the incidence of adverse clinical events among recipient as both groups recorded similar events. However, non-recipients of TH reported a significantly higher incidence of hypotension and GI bleeding in comparison to the recipients of TH and required vasopressor support ($P<0.05$) (tables 2 and 3). Similar observations were recorded by Bharadwaj et al. (10), Catherine et al. (17), and Joy et al. (23) reporting that the recipients of TH lacked a higher incidence of adverse clinical events, compared to

non-recipients.

In the present study, a smaller number of recipients of TH progressed from moderate to severe encephalopathy (n=5) in comparison to non-recipients (n=11) (P<0.05) (Table 3). Similarly, Shankaran et al. (24) reported that deterioration (encephalopathy from moderate to severe) was less observed among recipients.

In the present study, the mortality rate was 15% lower in recipients than in non-recipients (P<0.05). Similar observations regarding the difference in mortality rate between the two groups were recorded in studies conducted by Bharadwaj et al. (10) (21%), Catherine et al. (17) (6%), and Joy et al. (23) (5.1%) that the TH group had a lower rate of mortality in comparison to the non-TH group; nevertheless, the reduction in death rate was not statistically significant probably due to the smaller sample size. Nonetheless, the results of a recent RCT carried out by Weeke et al. (25) with a larger sample showed a reduction in death rate by 16.5% in participants, compared to non-recipients (P<0.05), which was in line with our findings. Based on the results of a Cochrane review (2013) (6) from 11 RCTs (n=1,505 infants), TH was beneficial in term and late preterm newborns with HIE, which significantly reduced the mortality rate without increasing major disability in survivors. Accordingly, the benefits of cooling on survival and neurodevelopment outcomes outweighed the short-term adverse effects.

In the present research, at the time of discharge, it was observed that recipients had better neurological outcomes as assessed by the HNNE scale. Moreover, they had less frequency of seizures and less requirement of anti-epileptics during NICU and at discharge in comparison to non-recipients. The recipient had lower mean hospitalization length in the NICU and had more chances of successful breastfeeding at discharge probably owing to the better neurological outcome at discharge (Table 4). Similar observations were recorded in other studies (17, 26, 27).

These positive neurodevelopmental outcomes have been attributed to reduced oxidative stress that results in better neurological outcomes at discharge and significantly less incidence of seizures in the hypothermia group according to results of studies performed by Joy et al. (23) and Gane et al. (27), in which the effect of TH was evaluated on oxidative stress by comet assay and 8-hydroxydeoxyguanosine. Deoxyribonucleic acid (DNA) damage is caused by a direct attack by reactive oxygen species that are overproduced during secondary re-perfusion injury and leads to the alteration of genetic material and cell death. The neuroprotective effect of TH against HIE can be attributed to its inhibitory actions on harmful cellular mechanisms induced by cerebral ischemic insult (28).

Considering our limited experience and the first step in using TH for perinatal asphyxia, our results are highly encouraging for feasibility and safety of TH administration in asphyxiated neonates since this method led to decreased mortality, better neurological outcome, fewer episodes of seizures, reduced need for anti-epileptics, and better prospects of breastfeeding at discharge at a resource-limited setting. One of the limitations of this study was related to its type, which was an RTC making our conclusions less reliable. Moreover, since it was a single-center study with a relatively smaller number of patients, only a limited number of neonates could have been enrolled and assessed in a relatively short time. In this regard, it is necessary to conduct further RCT studies with a larger sample size and long-term follow-up to confirm these results.

Conclusion

In the present study, it was concluded that TH administration for asphyxiated newborns using the low-cost cooling device with limited resources, was effective with positive neurodevelopment outcomes among recipients, without increasing adverse events. Considering the available national and international data, depriving an asphyxiated newborn of the opportunity to receive TH is a significant therapeutic failure, and the implementation of this therapy, especially in tertiary care centers fighting with the heavy burden of perinatal asphyxia, TH need to be a medical priority to reduce the burden of mortality and cerebral palsy. Based on our results, the TH protocol can be an effective modality to manage perinatal asphyxia even in a limited-resource setting. Simultaneously, the improvement of infrastructure, including neonatal transport, institutional deliveries, training programs development, and effective implementation of protocols, can further improve its beneficial outcome.

Acknowledgments

None.

Conflicts of interest

None.

References

1. Lawn JE, Cousens S, Zupan J; Lancet Neonatal Survival Steering Team. 4 million neonatal deaths: when? Where? Why? Lancet. 2005; 365(9462):891-900.
2. National neonatology forum (2002–2003). Indian National Neonatal Perinatal Database. Available at: URL: http://www.newbornwhocc.org/pdf/nnpd_ report_2002-03.PDF; 2003.
3. Robertson CM, Finer NN. Long-term follow-up of term neonates with perinatal asphyxia. Clin Perinatol. 1993; 20(2):483-500.
4. Pin TW, Eldridge B, Galea MP. A review of developmental outcomes of term infants with post-asphyxia neonatal encephalopathy. Eur J Paediatr Neurol. 2009; 13(3):224-34.
5. Committee on Fetus and Newborn, Papile LA, Baley JE, Benitz W, Cummings J, et al. (2014) Hypothermia and neonatal encephalopathy. Pediatrics 133: 1146-1150.
6. 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; 2013(1):CD003311.
7. Thayyil S, Costello A, Shankaran S, Robertson NJ. Therapeutic hypothermia for neonatal encephalopathy implications for neonatal units in India. Indian Pediatr. 2009; 46(4):283-9.
8. Pauliah SS, Shankaran S, Wade A, Cady EB, Thayyil S. Therapeutic hypothermia for neonatal encephalopathy in low- and middle-income countries: a systematic review and meta-analysis. PLoS One. 2013; 8(3):e58834.
9. Prashantha YN, Suman Rao PN, Nesargi S, Chandrakala BS, Balla KC, Shashidhar A. Therapeutic hypothermia for moderate and severe hypoxic ischaemic encephalopathy in newborns using low-cost devices - ice packs and phase changing material. Paediatr Int Child Health. 2019; 39(4):234-9.
10. Bharadwaj SK, Bhat BV. Therapeutic hypothermia using gel packs for term neonates with hypoxic ischaemic encephalopathy in resource-limited settings: a randomized controlled trial. J Trop Pediatr. 2012; 58(5):382-8.
11. Thomas N, Abiramalatha T, Bhat V, Varanattu M, Rao S, Wazir S, et al. Phase changing material for therapeutic hypothermia in neonates with hypoxic ischemic encephalopathy - a multi-centric study. Indian Pediatr. 2018; 55(3):201-5.
12. Thomas N, George KC, Sridhar S, Kumar M, Kuruvilla KA, Jana AK. Whole body cooling in newborn infants with perinatal asphyxial encephalopathy in a low resource setting: a feasibility trial. Indian Pediatr. 2011; 48(6):445-51.
13. Thayyil S, Oliveira V, Lally PJ, Swamy R, Bassett P, Chandrasekaran M, et al. Hypothermia for encephalopathy in low and middle-income countries (HELIX): study protocol for a randomised controlled trial. Trials. 2017; 18(1):432.
14. Shankaran S, Laptook AR, Ehrenkranz RA, Tyson JE, McDonald SA, Donovan EF, et al. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. N Engl J Med. 2005; 353(15):1574-84.
15. Dubowitz L, Mercuri E, Dubowitz V. An optimality score for the neurologic examination of the term newborn. J Pediatr. 1998; 133(3):406-16.
16. Romeo DM, Ricci D, Brogna C, Mercuri E. Use of the hammersmith infant neurological examination in infants with cerebral palsy: a critical review of the literature. Dev Med Child Neurol. 2016; 58(3):240-5.
17. Catherine RC, Ballambattu VB, Adhisivam B, Bharadwaj SK, Palanivel C. Effect of therapeutic hypothermia on the outcome in term neonates with hypoxic ischemic encephalopathy-a randomized controlled trial. J Trop Pediatr. 2021; 67(1):fmaa073.
18. Jacobs SE, Morley CJ, Inder TE, Stewart MJ, Smith KR, McNamara PJ, et al. Whole-body hypothermia for term and near-term newborns with hypoxic-ischemic encephalopathy: a randomized controlled trial. Arch Pediatr Adolesc Med. 2011; 165(8):692-700.
19. Thayyil S, Ayer M, Guhan B, Marlow N, Shankaran S, Robertson N. Whole body cooling using phase changing material in neonatal encephalopathy: A pilot randomised control trial. Pediatr Acad Soc Meet. 2010; 9:43506.
20. Cotten CM, Shankaran S. Hypothermia for hypoxic–ischemic encephalopathy. Exp Rev Obstet Gynecol. 2010; 5(2):227-39.
21. Roberts CT, Stewart MJ, Jacobs SE. Earlier initiation of therapeutic hypothermia by non-tertiary neonatal units in victoria, Australia. Neonatology. 2016; 110(1):33-9.
22. Azzopardi DV, Strohm B, Edwards AD, Dyet L, Halliday HL, Juszczak E, et al. Moderate hypothermia to treat perinatal asphyxial encephalopathy. N Engl J Med. 2009; 361(14): 1349-58.
23. Joy R, Pournami F, Bethou A, Bhat VB, Bobby Z. Effect of therapeutic hypothermia on oxidative stress and outcome in term neonates with perinatal asphyxia: a randomized controlled trial. J Trop Pediatr. 2013; 59(1):17-22.
24. 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 Pediatr. 2012; 160(4):567-72.e3.
25. Weeke LC, Groenendaal F, Mudigonda K, Blennow M, Lequin MH, Meiners LC, et al. A novel magnetic resonance imaging score predicts neurodevelopmental outcome after perinatal asphyxia and therapeutic hypothermia. J Pediatr. 2018; 192:33-40.e2.
26. Orbach SA, Bonifacio SL, Kuzniewicz MW, Glass HC. Lower incidence of seizure among neonates treated with therapeutic hypothermia. J Child Neurol. 2014; 29(11):1502-7.
27. Gane BD, Bhat V, Rao R, Nandhakumar S, Harichandrakumar KT, Adhisivam B. Effect of therapeutic hypothermia on DNA damage and neurodevelopmental outcome among term neonates with perinatal asphyxia: a randomized controlled trial. J Trop Pediatr. 2014; 60(2):134-40.
28. Ji X, Luo Y, Ling F, Stetler RA, Lan J, Cao G, et al. Mild hypothermia diminishes oxidative DNA damage and pro-death signaling events after cerebral ischemia: a mechanism for neuroprotection. Front Biosci. 2007; 12:1737-47.
29. Orbach SA, Bonifacio SL, Kuzniewicz MW, Glass HC. Lower incidence of seizure among neonates treated with therapeutic hypothermia. J Child Neurol. 2014; 29(11):1502-7.
30. Gane BD, Bhat V, Rao R, Nandhakumar S, Harichandrakumar KT, Adhisivam B. Effect of therapeutic hypothermia on DNA damage and neurodevelopmental outcome among term neonates with perinatal asphyxia: a randomized controlled trial. J Trop Pediatr. 2014; 60(2):134-40.
31. Ji X, Luo Y, Ling F, Stetler RA, Lan J, Cao G, et al. Mild hypothermia diminishes oxidative DNA damage and pro-death signaling events after cerebral ischemia: a mechanism for neuroprotection. Front Biosci. 2007; 12:1737-47.