Therapeutic hypothermia in the management of perinatal asphyxia: Evidence and experience at TUTH

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- Outline of presentation
  - Definition and epidemiology
  - Pathophysiology and basis of management
  - Experience of Therapeutic hypothermia at TUTH
  - Therapeutic hypothermia in LMIC
  - Conclusion

Organization	Definition
World Health Organization	Failure to initiate and sustain breathing
NNPD Network	• Moderate PA: Slow/gasping breathing or an Apgar score of 4 to 6 at 1 minute • Severe PA: No breathing or an Apgar score of 0-3 at 1 minute of age • Community- absence of cry at 1 min and severe asphyxia as absent or inadequate breathing at five minutes
American Academy of Pediatrics and American College of Obstetrics and Gynecology	Presence of all of following criteria: • Profound metabolic or mixed acidemia (pH< 7.00) in umbilical cord blood • Persistence of low Apgar scores ≤ 3 for more than 5 minutes • Signs of neonatal neurologic dysfunction (e.g., seizures, encephalopathy, tone abnormalities) • Evidence of multiple organ involvement (such as that of kidneys, lungs, liver, heart and intestine).

EPIDEMIOLOGY

- Significant contributor for neonatal mortality worldwide and neonatal encephalopathy.
- Incidence of HIE is approximately
  - 1–3:1000 term/near-term live births in high-resource countries
  - 31:1000 live births in low-resource settings.

How common is this condition in Nepal?

- 6 per 1000 term live births *. (government funded 12 hospitals)
- Tertiary care referral hospital of 3.66 %
  - 1.3% incidence of moderate and severe asphyxia
  - case fatality rate of 7%**.
- Perinatal asphyxia comprises 16.83% of NICU admission***.

*Sunny et al. BMC Pediatrics(2021) 21:394

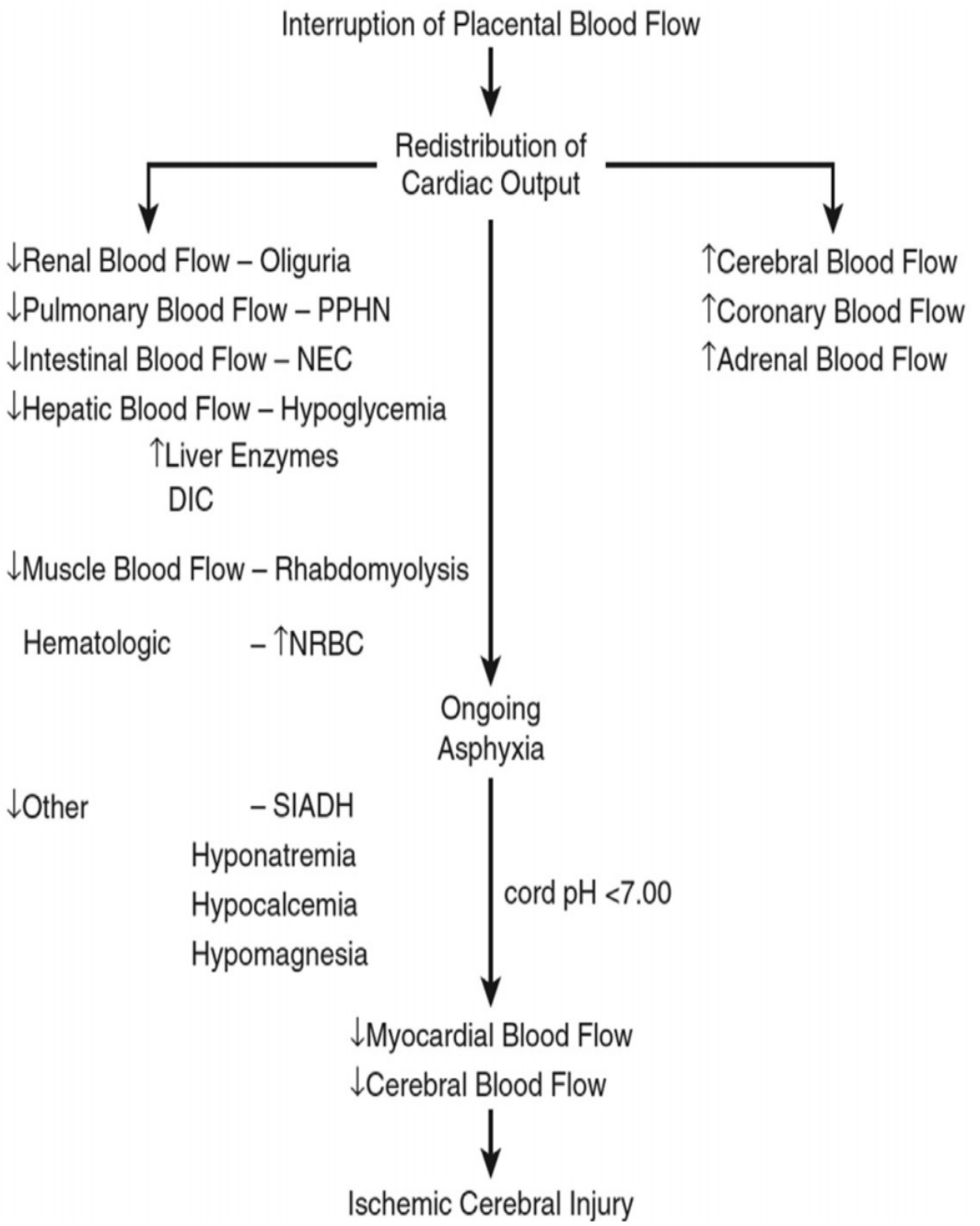
**Manandhar, S. R., & Basnet, R. (2019). Prevalence of Perinatal Asphyxia in Neonates at a Tertiary Care Hospital: A Descriptive Cross-sectional Study. *Journal of Nepal Medical Association*, *57*(219). https://doi.org/10.31729/jnma.4550

***Niranjan Bhandari , Nimish Joshi, Sachi Adhikari, Pankaj Kumar Singh and Nitesh Shrestha World Journal of Advanced Research and Reviews, 2022, 15(02), 557–561

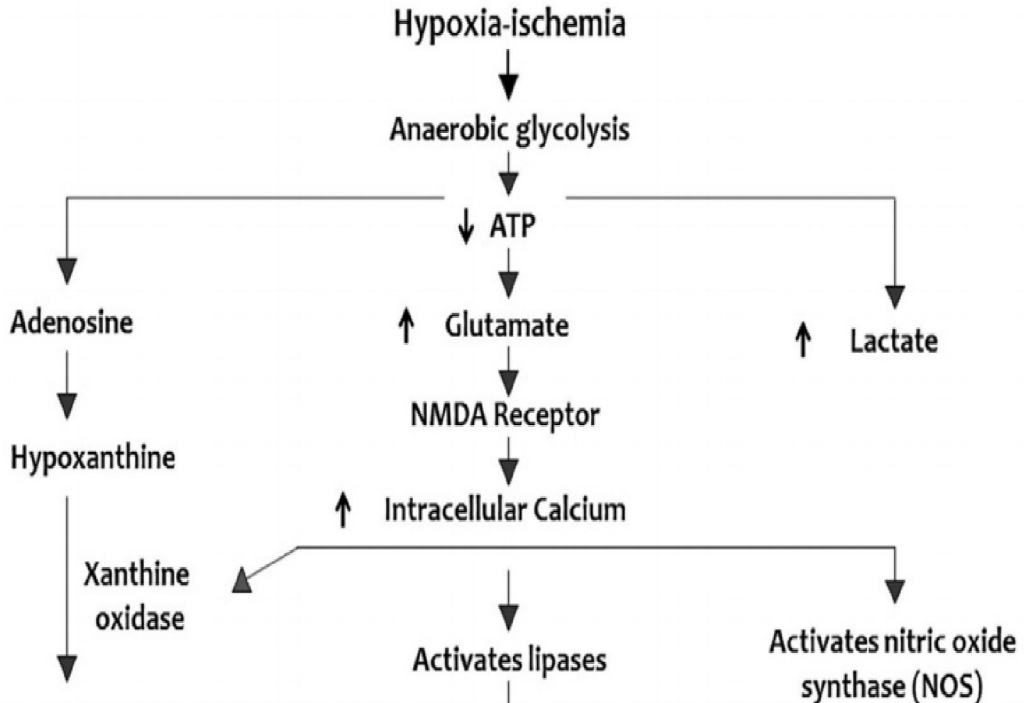
PATHOPHYSIOLOGY OF PERINATAL ASPHYXIA

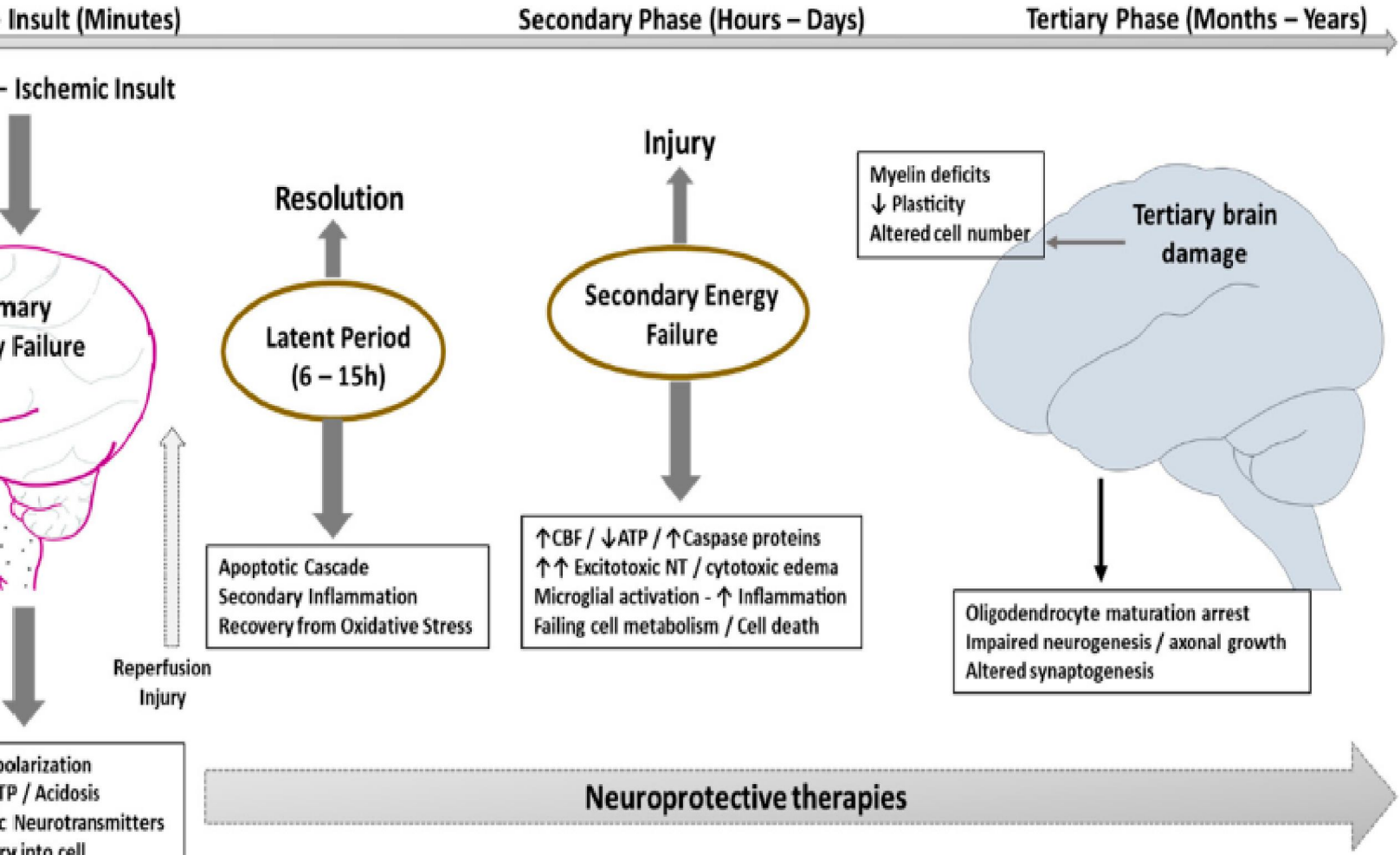
- Hypoxia-ischemia leads to physiologic and biochemical changes
- Diving reflex
- Shunting of blood within the brain

CIRCULATORY CHANGES AFTER ASPHYXIA



BIOCHEMICAL CHANGES AFTER ASPHYXIA




Insult (Minutes)
Secondary Phase (Hours – Days)
Tertiary Phase (Months – Years)
- Ischemic Insult
mary
Failure
Resolution
Latent Period
(6 – 15h)
Apoptotic Cascade
Secondary Inflammation
Recovery from Oxidative Stress
Reperfusion
Injury
Injury
Secondary Energy
Failure
↑CBF / ↓ATP / ↑Caspase proteins
↑↑ Excitotoxic NT / cytotoxic edema
Microglial activation - ↑ Inflammation
Failing cell metabolism / Cell death
Myelin deficits
↓ Plasticity
Altered cell number
Tertiary brain
damage
Oligodendrocyte maturation arrest
Impaired neurogenesis / axonal growth
Altered synaptogenesis
polarization
TP / Acidosis
c Neurotransmitters
Neuroprotective therapies

Effectiveness of therapeutic hypothermia

Therapeutic hypothermia (TH)

- `standard of care' for infants with moderate severe encephalopathy following perinatal asphyxia in High income countries (HIC).'
- 35% reduction in neonatal mortality (RR 0.64,95% 0.51-0.81).*

Challenges to implementing therapeutic hypothermia in our setting

- the lack of resources, including the necessary equipment and trained personnel.

Mechanism of TH

non-specific neuro -protective therapy.

reduction in cerebral metabolism

- slows cell depolariza-tion
- reduces accumulation of excito-toxic neuro-transmitters
- suppresses oxygen free radical release
- lipid peroxidation of cell membranes.

suppresses apoptotic processes in the developing ain

suppress the release of pro-inflammatory cyto -

Recommendation

The International Liaison Committee on Resuscitation and the American Heart Association in their 2020 guidelines recommend that TH should be provided under defined protocols similar to those used in published clinical trials and in facilities capable of multidisciplinary care and

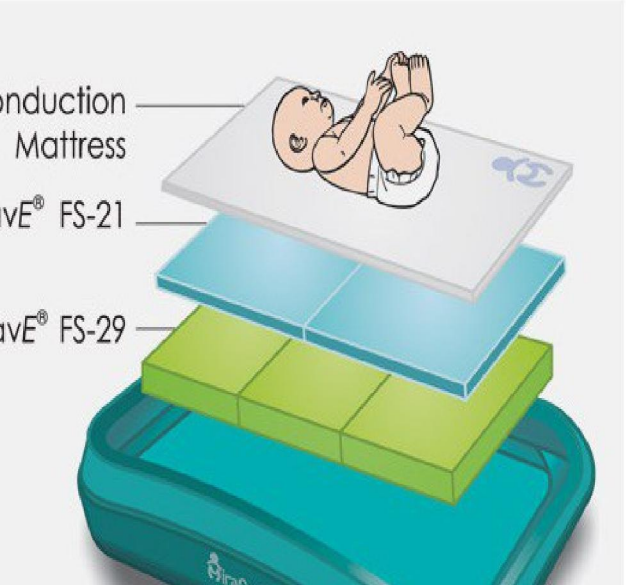
Methods for TH

Head cooling/Whole body cooling

ce/gel packs or phase change material (PCM)

Servo controlled device/ Non servo controlled

THERAPEUTIC HYPOTHERMIA



CRITERIA FOR THERAPEUTIC HYPOTHERMIA:

≥ 35 weeks gestational age and more than 1.8kgs. (If gestational e is not known, baby's weight should be at least 2kg.

< 6hrs post birth.

Evidence of asphyxia as defined by the presence of any of the llowing criteria:

i. Apgar ≤5 or absence of cry at 5 minutes of life or continued need for resuscitation with positive pressure ventilation +/- chest compressions at 5 minutes of age

ii. Cord pH <7.0 or base deficit of 12 or more within 60 minutes of birth

CRITERIA FOR THERAPEUTIC HYPOTHERMIA:

Presence of any of the following features of encephalopathy

a) Clinical seizures

b) Altered state of consciousness (lethargy, stupor or coma) and any one of the following

i) Hypotonia

ii) Abnormal reflexes including oculomotor or pupillary abnormalities

iii) Absent or weak suck

CONTRAINDICATIONS

onates with following conditions should not be nsidered for TH:

- Major congenital malformations
- Suspected/known chromosomal disorder
- Clinical and echocardiographic evidence of PPHN
- Active bleeding

DURATION AND TEMPERATURE MONITORING IN TH

Aim of cooling → achieve the target temperature within 30 minute of commencement

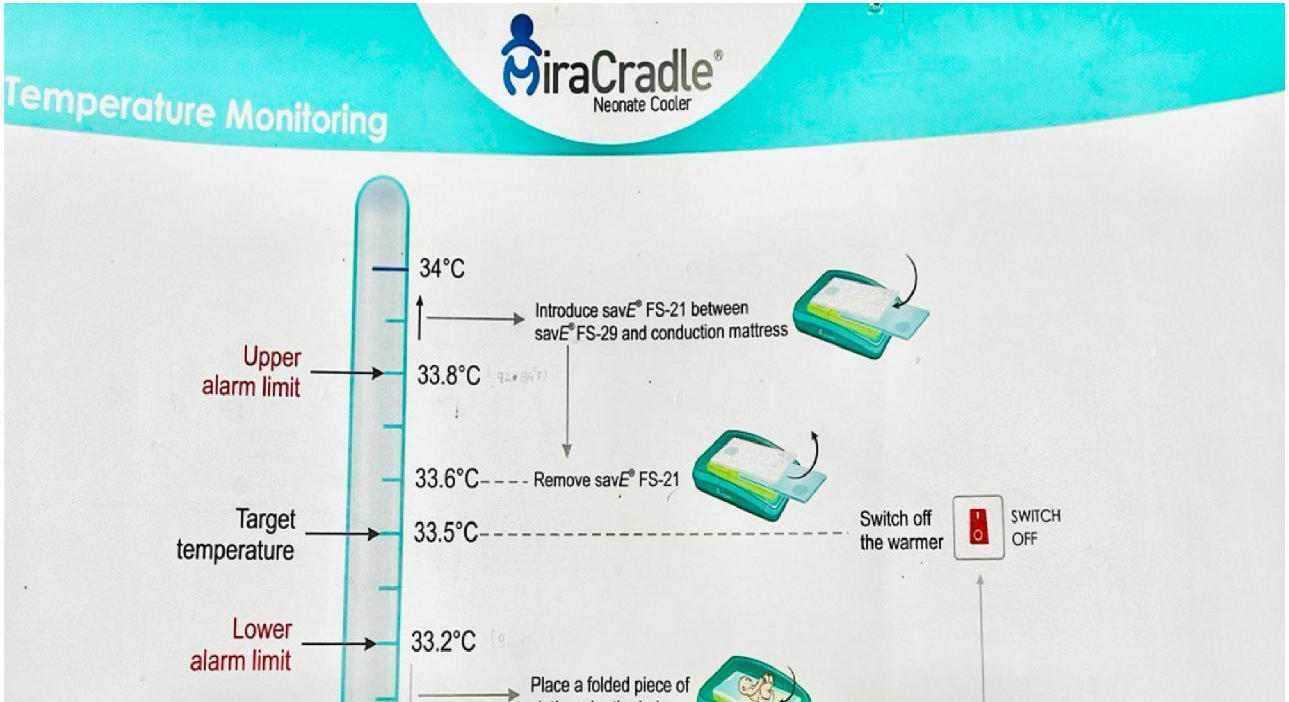
Target rectal temperature is between 33.2°C – 33.8°C

The total period is **84 hours**, consists of 2 phases:

a) Active cooling- for 72 hours from the initiation of cooling

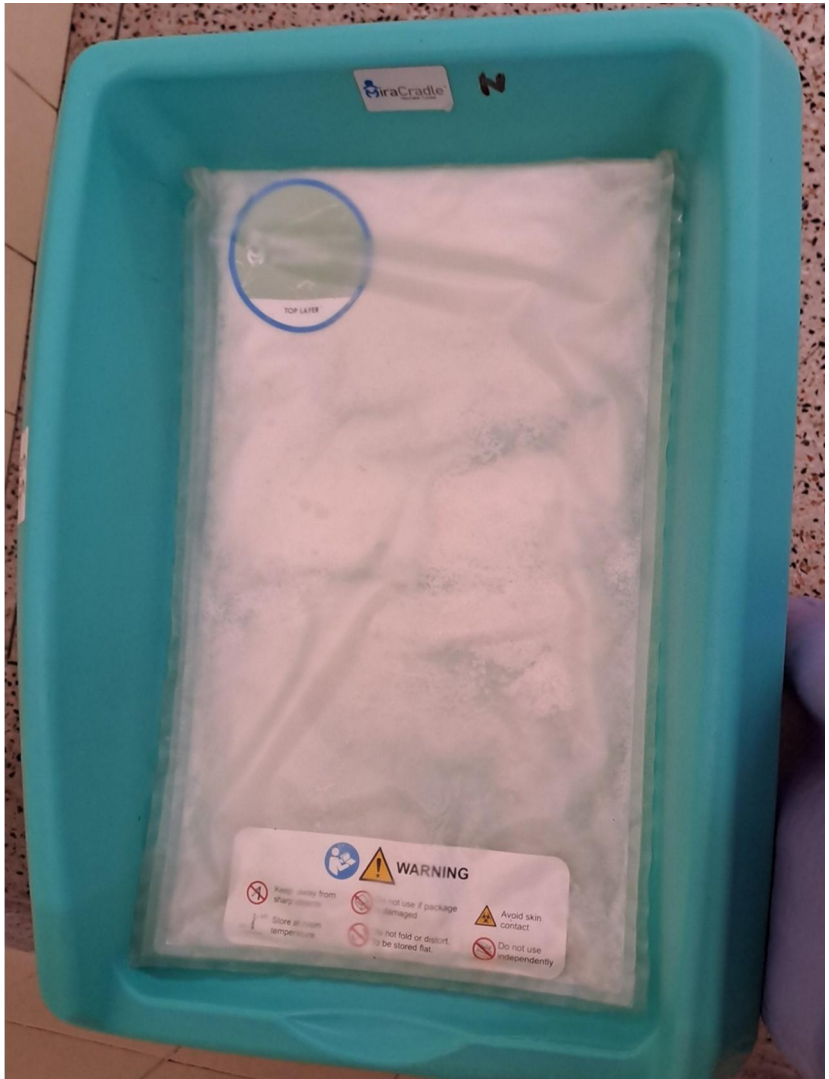
b) Rewarming- 12 hours of active gradual rewarming time after completion of 72hrs of cooling.

EMPERATURE MONITORING IN TH

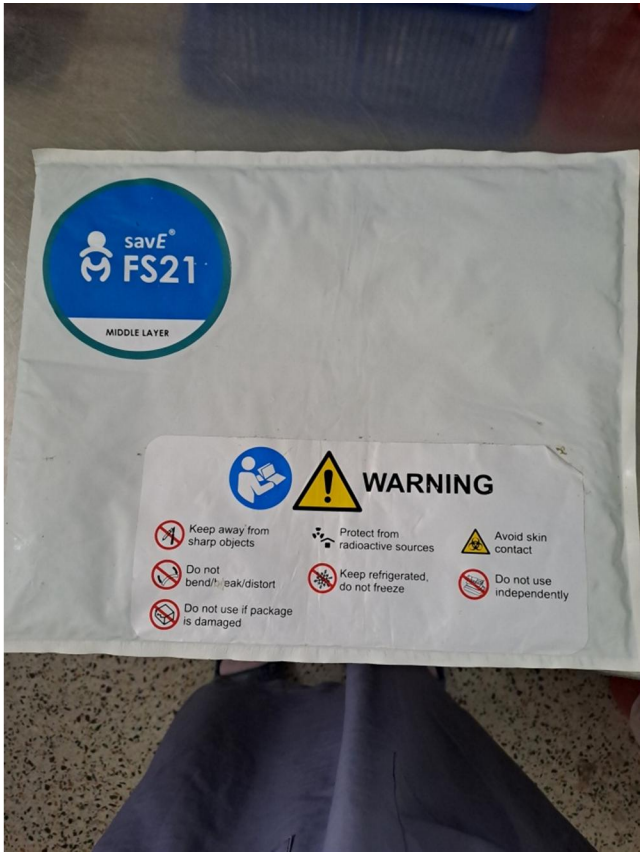


MONITORING DURING TH

ests	Baseline	24 hours	48 hours	72 hours
ctrolytes		√		√
/Creatine		√		√
PTT	√		√	
	√		√	√
T/SGPT	√			


BiraCradle
TOP LAYER
WARNING
Avoid skin contact
Do not use independently


savE
FS29
BOTTOM LAYER
savE
FS29
BOTTOM LAYER
savE
FS29
BOTTOM LAYER


savE
FS21
MIDDLE LAYER
WARNING
Keep away from sharp objects
Protect from radioactive sources
Avoid skin contact
Do not bend/break/distort
Keep refrigerated, do not freeze
Do not use independently
Do not use if package is damaged

Result

Total 20 cases (chaitra 2078- asoj 2080)

Excluded
2 cases HIE 1

18 cases analyzed

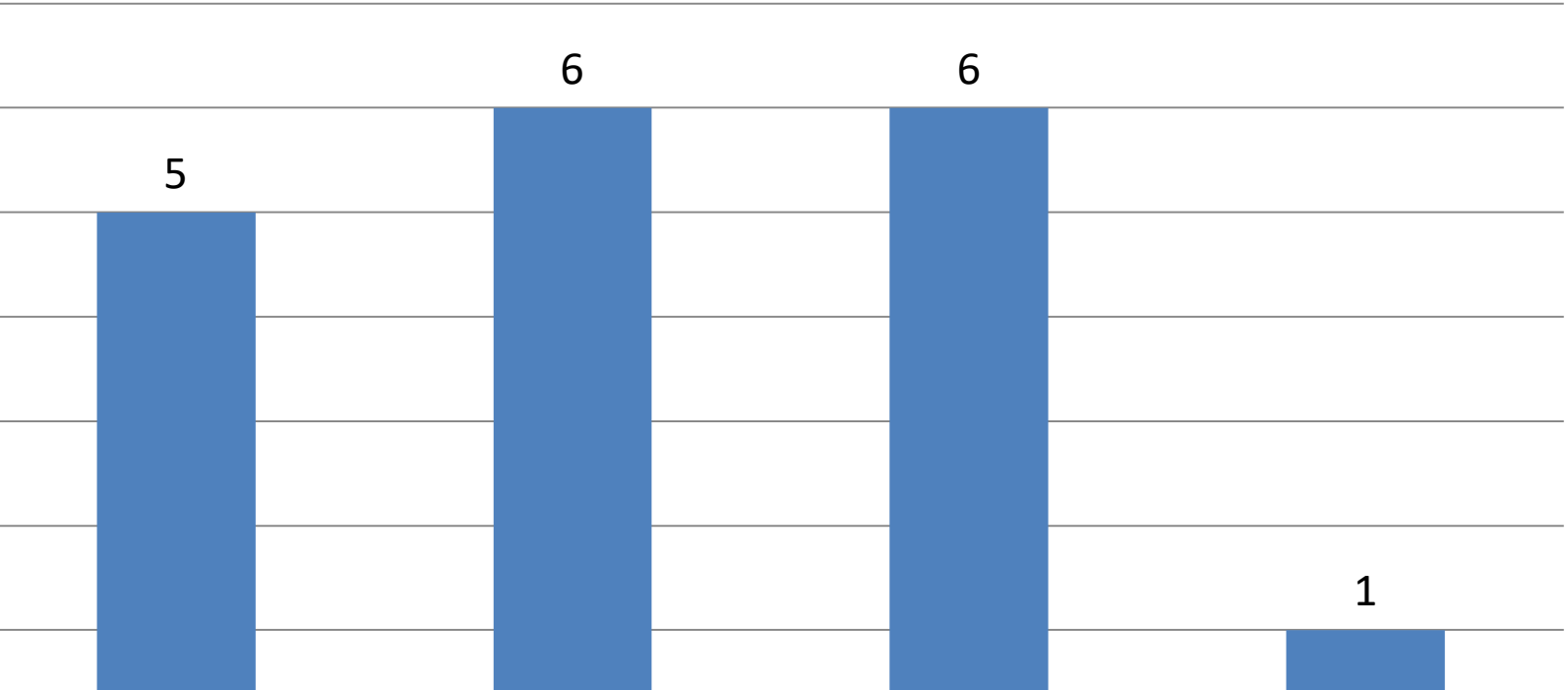
Maternal clinical profile

aternal age **-30** **0-35**	**N =18 (100%)** **9 (50 %)** **9(50%)**
G 7week -40 0	 1(5.5%) 15 (83.33%) 2(11%)
mi cond rd &above	7(38.9 %) 7 (38.9 %) 4 (22.22%)
aternal riskfactors sent e ore than one	 7 (38.9%) 1 (5.6%) 10 (55.55%)
ode of delivery	

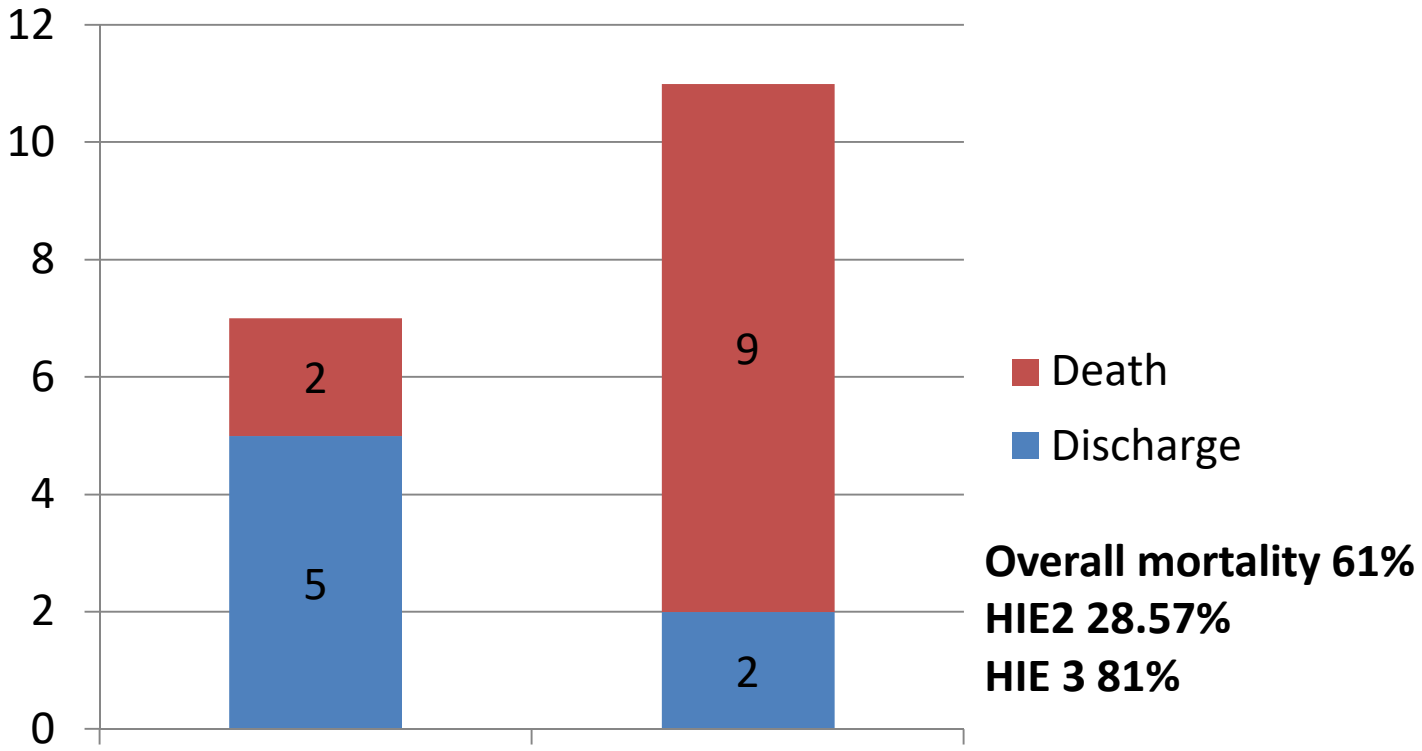
Clinical profile of newborn

weight (Kg) **± SD**	**3.12 ± 0.45**
of delivery le TUTH	 9 (50 %) 9 (50 %)
upport 	 1 (5.6%) 5 (27.8%) 12 (66.7%)
   	 7 (38.9%) 11 (61.11%)
pH (14) ± SD	 6.8 ± 0.24
dysfunction	

Resuscitation at birth

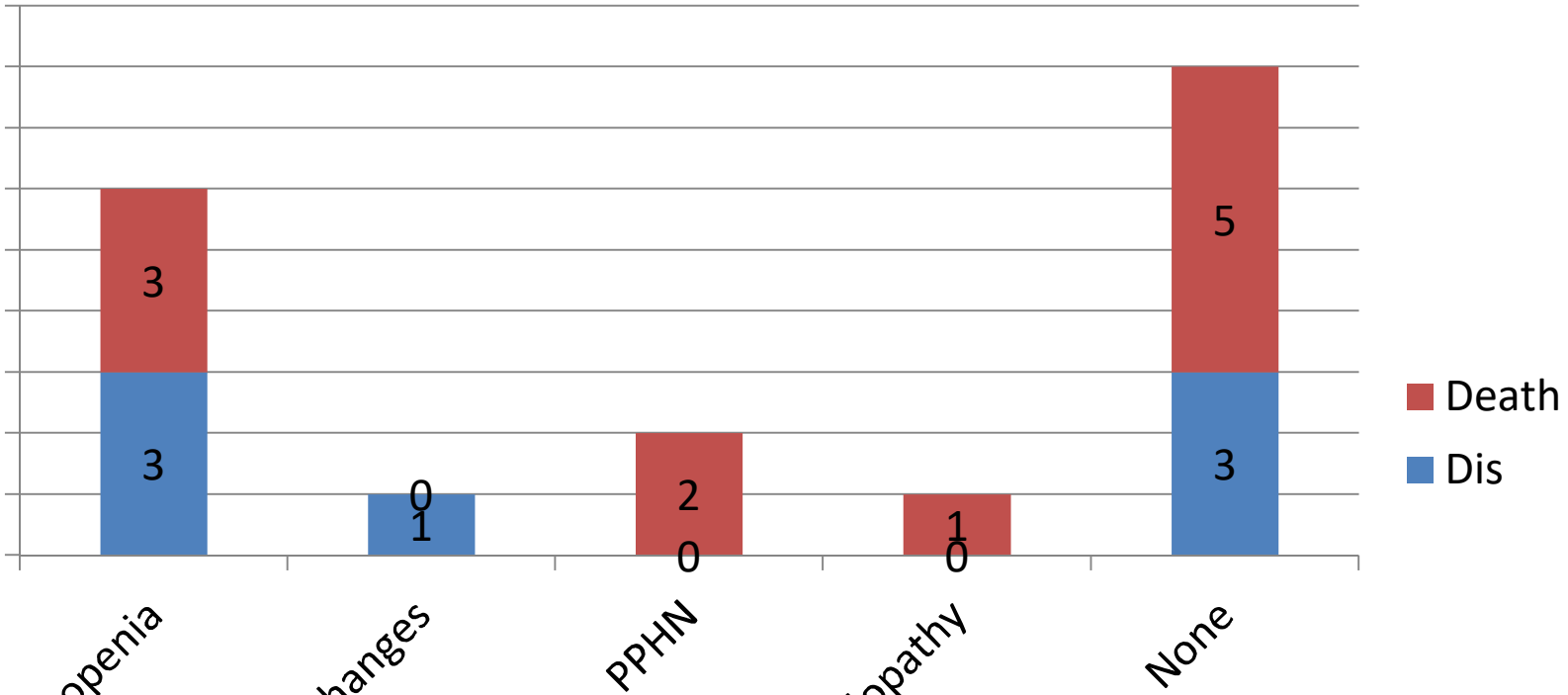


Outcome according to severity of HIE



Overall mortality 61%
HIE2 28.57%
HIE 3 81%

Adverse effect and outcome



	Mean ± SD
n Duration of Hospital stay in days 7	12.57 ± 4.721
at Death in hrs 1	86.11 ± 165.331

OUTCOME OF INFANTS WITH PERINATAL ASPHYXIA

The overall mortality rate is 20%.

Neurodevelopmental sequelae in surviving ranges from 30% to 50%.

Risk of cerebral palsy is 5% to 10%

Severity of encephalopathy is a better predictor of outcome.

- Mild HIE: 1% mortality, 98% to 100%→ normal neurologic outcome
- Moderate HIE: 5-10 % mortality, 20% to 30% have abnormal neurodevelopmental outcome

Encephalopathy in Low- and Middle-Income Countries: A Literature Review

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ABSTRACT

Aims: This structured review aimed to discuss the existing literature on therapeutic hypothermia for moderate to severe neonatal encephalopathy exclusively in low- and middle-income countries (LMICs).

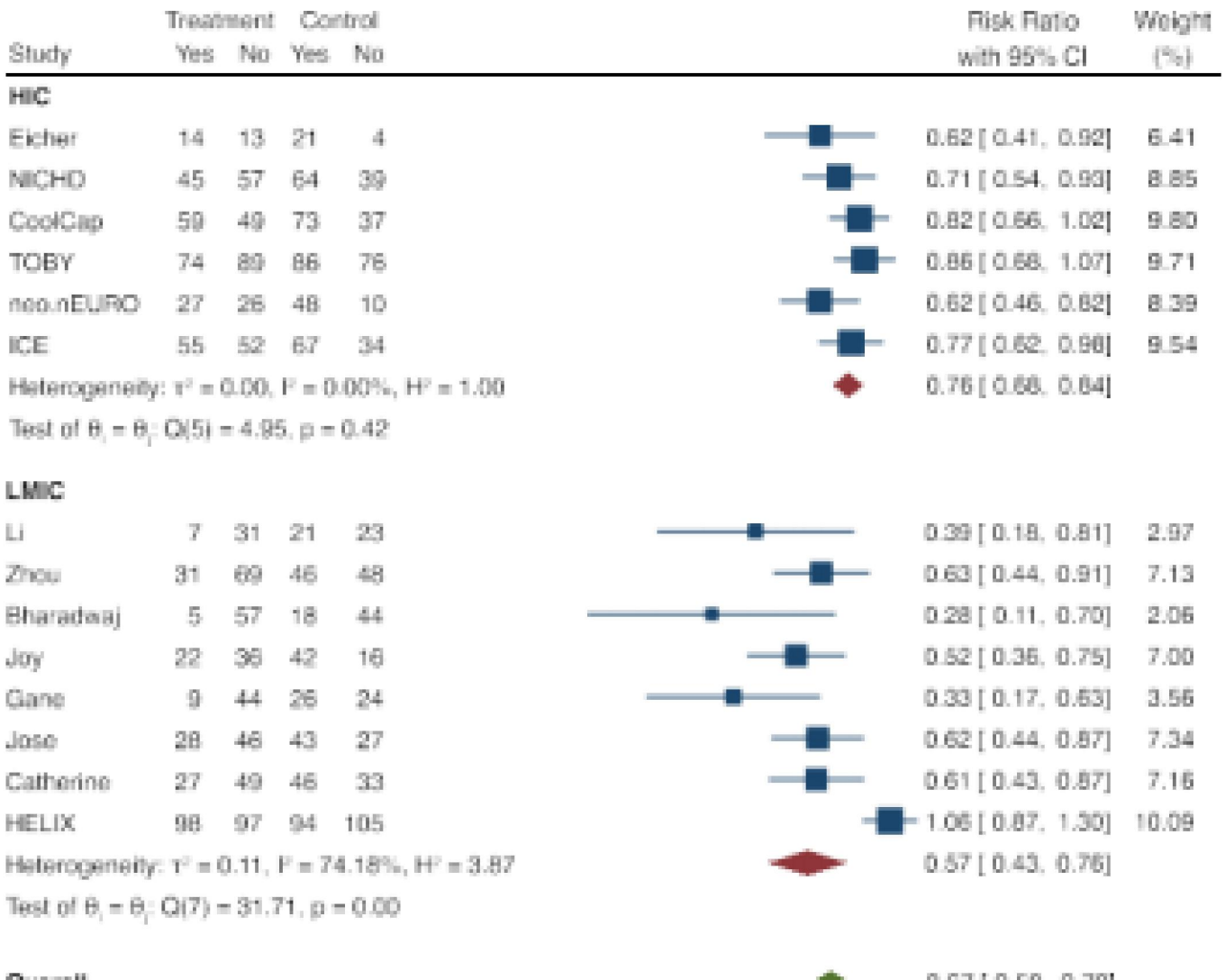
Methods: Medline, Embase, CINHAL and Cochrane Registry were searched for original papers with therapeutic hypothermia (TH) for treating neonatal encephalopathy in LMIC with no language restrictions. The search identified 1413 papers from 1990 to 31 August 2021.

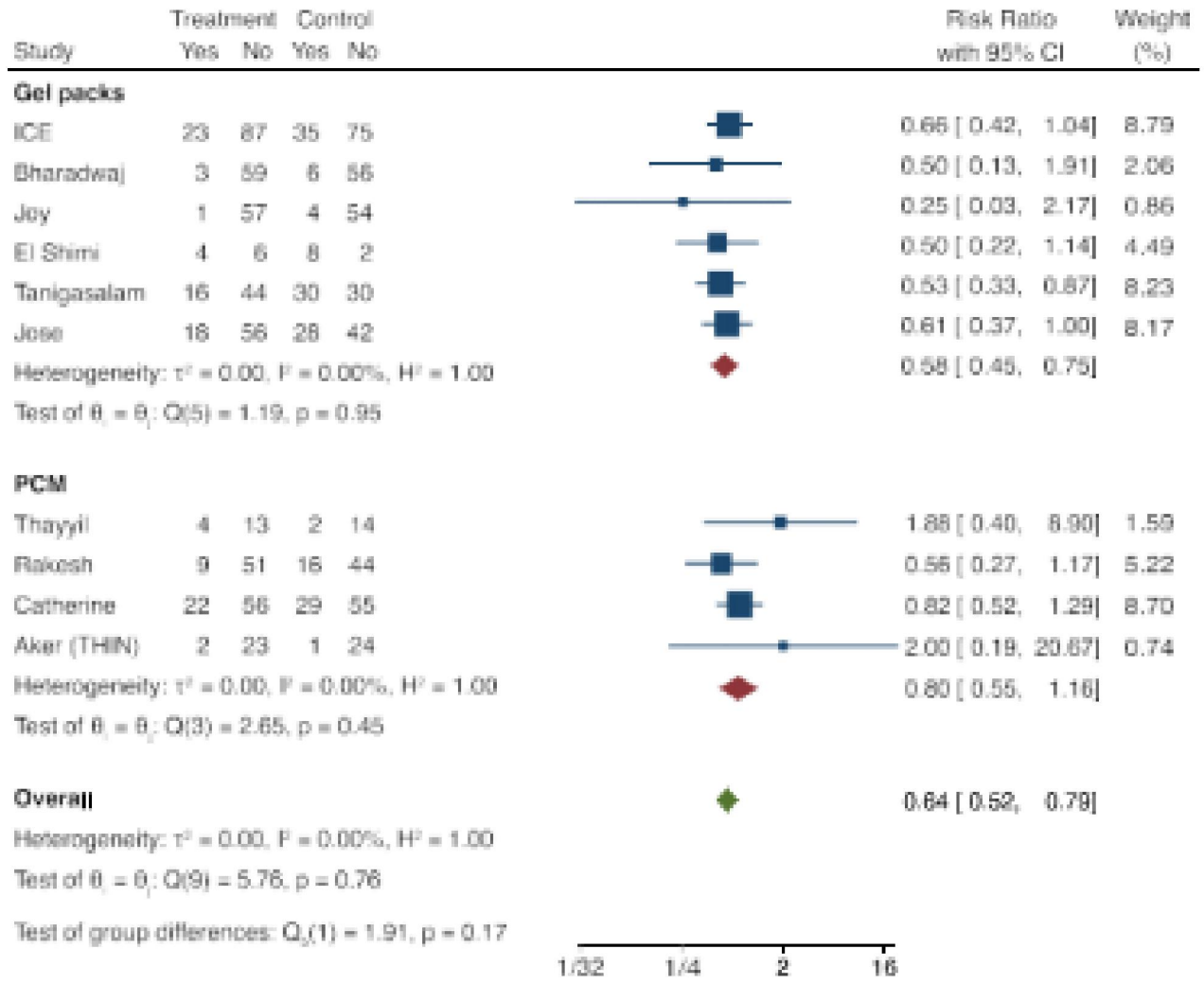
Results: Twenty-one original papers were included after duplicates removal and full-text screening in the final review. Fourteen randomized control studies and seven non-randomized studies were discussed with various modes of cooling (servo-controlled, phase changing material, traditional methods), complications during cooling, mortality and long-term neurodevelopmental assessment.

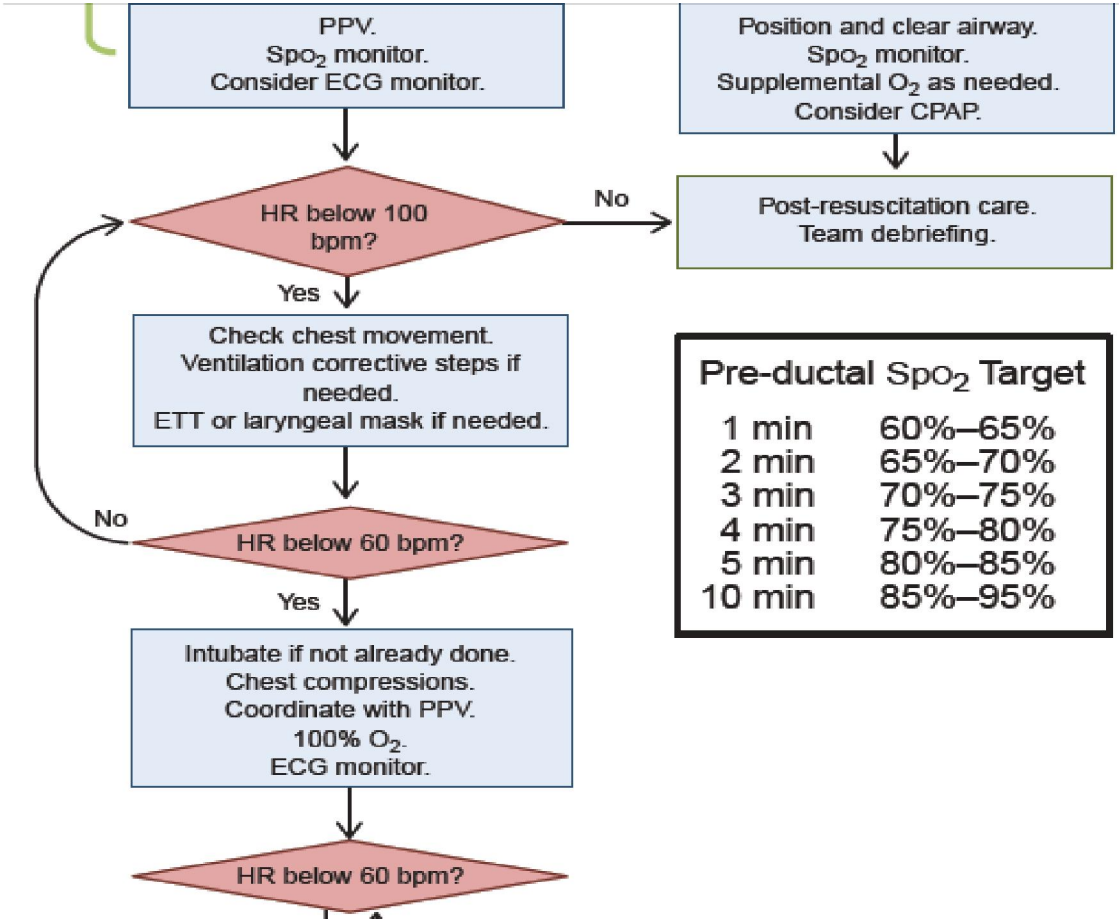
s We did a multicountry open-label, randomised controlled trial in seven tertiary neonatal intensive care units in ri Lanka, and Bangladesh. We enrolled infants born at or after 36 weeks of gestation with moderate or severe l encephalopathy and a need for continued resuscitation at 5 min of age or an Apgar score of less than 6 at 5 min for babies born in a hospital), or both, or an absence of crying by 5 min of age (for babies born at home). Using ased randomisation system, we allocated infants into a group receiving whole body hypothermia (33·5°C) for ing a servo-controlled cooling device, or to usual care (control group), within 6 h of birth. All recruiting sites had s for invasive ventilation, cardiovascular support, and access to 3 Tesla MRI scanners and spectroscopy. Masking intervention was not possible, but those involved in the magnetic resonance biomarker analysis and evelopmental outcome assessments were masked to the allocation. The primary outcome was a combined nt of death or moderate or severe disability at 18–22 months, assessed by the Bayley Scales of Infant and Toddler pment (third edition) and a detailed neurological examination. Analysis was by intention to treat. This trial is ed with ClinicalTrials.gov, NCT02387385.

s We screened 2296 infants between Aug 15, 2015, and Feb 15, 2019, of whom 576 infants were eligible for on. After exclusions, we recruited 408 eligible infants and we assigned 202 to the hypothermia group and 206 to trol group. Primary outcome data were available for 195 (97%) of the 202 infants in the hypothermia group and %) of the 206 control group infants. 98 (50%) infants in the hypothermia group and 94 (47%) infants in the group died or had a moderate or severe disability (risk ratio 1·06; 95% CI 0·87–1·30; p=0·55). 84 infants (42%) ypothermia group and 63 (31%; p=0·022) infants in the control group died, of whom 72 (36%) and 49 (24%; 87) died during neonatal hospitalisation. Five serious adverse events were reported: three in the hypothermia one hospital readmission relating to pneumonia, one septic arthritis, and one suspected venous thrombosis), o in the control group (one related to desaturations during MRI and other because of endotracheal tube ement during transport for MRI). No adverse events were considered causally related to the study intervention.

etation Therapeutic hypothermia did not reduce the combined outcome of death or disability at 18 months


Study
Treatment Yes No
Control Yes No
Risk Ratio with 95% CI
Weight (%)
HIC
Eicher 14 13 21 4 0.62 [0.41, 0.92] 6.41
NICHD 45 57 64 39 0.71 [0.54, 0.93] 8.85
CoolCap 59 49 73 37 0.82 [0.66, 1.02] 9.80
TOBY 74 89 86 76 0.86 [0.68, 1.07] 9.71
neo.nEURO 27 26 48 10 0.62 [0.46, 0.82] 8.39
ICE 55 52 67 34 0.77 [0.62, 0.96] 9.54
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00 0.76 [0.68, 0.84]
Test of θi = θj: Q(5) = 4.95, p = 0.42
LMIC
Li 7 31 21 23 0.39 [0.18, 0.81] 2.97
Zhou 31 69 46 48 0.63 [0.44, 0.91] 7.13
Bharadwaj 5 57 18 44 0.28 [0.11, 0.70] 2.06
Joy 22 36 42 16 0.52 [0.36, 0.75] 7.00
Gane 9 44 26 24 0.33 [0.17, 0.63] 3.56
Jose 28 46 43 27 0.62 [0.44, 0.87] 7.34
Catherine 27 49 46 33 0.61 [0.43, 0.87] 7.16
HELIX 98 97 94 105 1.06 [0.87, 1.30] 10.09
Heterogeneity: τ² = 0.11, I² = 74.18%, H² = 3.87 0.57 [0.43, 0.76]
Test of θi = θj: Q(7) = 31.71, p = 0.00


Study
Treatment Yes No
Control Yes No
Risk Ratio with 95% CI
Weight (%)
Gel packs
ICE 23 87 35 75 0.66 [0.42, 1.04] 8.79
Bharadwaj 3 59 6 56 0.50 [0.13, 1.91] 2.06
Joy 1 57 4 54 0.25 [0.03, 2.17] 0.86
El Shimi 4 6 8 2 0.50 [0.22, 1.14] 4.49
Tanigasalam 16 44 30 30 0.53 [0.33, 0.87] 8.23
Jose 16 56 28 42 0.61 [0.37, 1.00] 8.17
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00 0.58 [0.45, 0.75]
Test of θi = θj: Q(5) = 1.19, p = 0.95
PCM
Thayyil 4 13 2 14 1.88 [0.40, 8.90] 1.59
Rakesh 9 51 16 44 0.56 [0.27, 1.17] 5.22
Catherine 22 56 29 55 0.82 [0.52, 1.29] 8.70
Aker (THIN) 2 23 1 24 2.00 [0.19, 20.67] 0.74
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00 0.80 [0.55, 1.16]
Test of θi = θj: Q(3) = 2.65, p = 0.45
Overall 0.64 [0.52, 0.79]
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00
Test of θi = θj: Q(9) = 5.76, p = 0.76
Test of group differences: Qb(1) = 1.91, p = 0.17
1/32
1/4
2
16


PPV.
Spo2 monitor.
Consider ECG monitor.
HR below 100 bpm?
No
Position and clear airway.
Spo2 monitor.
Supplemental O2 as needed.
Consider CPAP.
Post-resuscitation care.
Team debriefing.
Yes
Check chest movement.
Ventilation corrective steps if needed.
ETT or laryngeal mask if needed.
No
HR below 60 bpm?
Yes
Intubate if not already done.
Chest compressions.
Coordinate with PPV.
100% O2.
ECG monitor.
HR below 60 bpm?
Pre-ductal Spo2 Target
1 min 60%–65%
2 min 65%–70%
3 min 70%–75%
4 min 75%–80%
5 min 80%–85%
10 min 85%–95%

NNF Position Statement and Guidelines For Use of Therapeutic Hypothermia to treat Neonatal Hypoxic Ischemic Encephalopathy In India October 2021

Where should Therapeutic Hypothermia be offered?

- TH is a therapy offered to sick neonates who need intensive care. Therefore, it is imperative that NICUs proposing to offer TH must have good quality NICU care reflected in their risk-adjusted outcomes.

Key message

- Therapeutic hypothermia is one of the neuroprotective strategy for prevention of death and disability due to perinatal asphyxia
- It might not be as effective as it has been observed in HIC and it has its own side effect
- Neonatal resuscitation in room air and based on target oxygen saturation might prevent free radical oxygen damage and severity of neuronal injury
- The acute treatment and long-term neurodevelopmental outcomes should be adequately evaluated before universal recommendation this

THANK YOU