NICHD
NEONATAL RESEARCH NETWORK

Randomized Trial of Targeted Temperature Management with Whole Body Hypothermia for Moderate and Severe Encephalopathy in Premature Infants 33-35 Wks Gestation – A Bayesian Study (aka *Preemie Hypothermia)*

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Disclosures

- Speaker: Roger G. Faix
- Dr. Faix has no financial relationships to disclose or Conflicts of Interest to resolve.
- This presentation will not involve discussion of unapproved, off-label, experimental or investigational use of a drug.
- Use of the Cincinnati Sub-Zero Blanketrol device was covered by an FDA-approved IDE

Background

- Perinatal hypoxic-ischemic (HI) injury is a major cause of brain injury at all gestational ages (GA)
- Only effective RCT evidence-based treatment for such injury in high income countries so far is therapeutic hypothermia
- Most supportive studies have been limited to infants **≥36 wks GA**

Therapeutic Hypothermia at <36 wks GA

- Two RCTs with follow-up at 12-24 mos (Eicher 2005; Jacobs 2011) included enrollment at 35^0-35^6 wks
  - Total randomized 35 wk infants: N = 7
    - Control: 1 death, 1 normal survivor
    - Cooled: 2 deaths, 2 survivors with moderate disability, **1 normal survivor**

DJ Eicher et al, Pediatr Neurol 2005, 32:11
SE Jacobs et al, Arch Pediatr Adolesc Med 2011, 165: 692

Therapeutic Hypothermia at <36 wks GA

- 'Therapeutic drift' has occurred for infants with GA <36 weeks, despite lack of evidence for efficacy and safety
- Infants with GA < 36 weeks may be at risk for increased prematurity-associated problems that may be triggered by or respond adversely to therapeutic hypothermia (e.g., major ICH*, NEC, coagulopathy, shock)

*grade 3 or 4 IVH, large intraparenchymal/cerebellar or midline shift

Primary Hypothesis

- Therapeutic hypothermia (esophageal temperature [Tes], 33.5°C) for 72 hrs will decrease death or moderate/severe disability at 18-22 months corrected age in infants 33^0 – 35^6 wks GA with moderate or severe encephalopathy at <6 hrs of age compared to infants treated with targeted normothermia (Tes, 37°C)

NCT01793129 at ClinicalTrials.gov

Inclusion Criteria

- Gestational age: 33^0 -35^6 weeks
- Postnatal age: < 6 h
- Severe acidosis and/or resuscitation at birth as per prior NRN hypothermia studies
- Moderate or severe encephalopathy* assessed by certified examiners **OR** clinical seizures at < 6 h

*Level of consciousness **must** be moderate or severe

Modified from S Shankaran et al, NEJM 2005;353:1574

Exclusion Criteria

- 'Core' temperature <34°C for >1hr at screening
- Paralytic, sedative agents obscure exam per examiner
- Encephalopathy unlikely to be hypoxic-ischemic
- Major anomaly
- Moribund and not receiving full intensive care
- Lack of clinician agreement

Randomized Temperature Management

- *Cooled group:* whole body cooling
  - Target Tes: 33.5°C (33.0-34.0°C) for 72 hours
  - Rewarming: 0.5°C/hr
- *Non-cooled group:*
  - Target Tes: 37°C (36.5-37.3°C)
  - Servo skin temp, adjust radiant warmer per Tes
  - Algorithm for Tes > 37.3°C

Safety

- Adverse events per prior NRN Hypothermia trials **plus** ICH, NEC, coagulopathy, dysglycemia
- Cranial ultrasound required within 24 h of randomization and brain MRI at 7-21 days
- DSMC reviewed cumulative acute outcomes and adverse events at 6 specified intervals

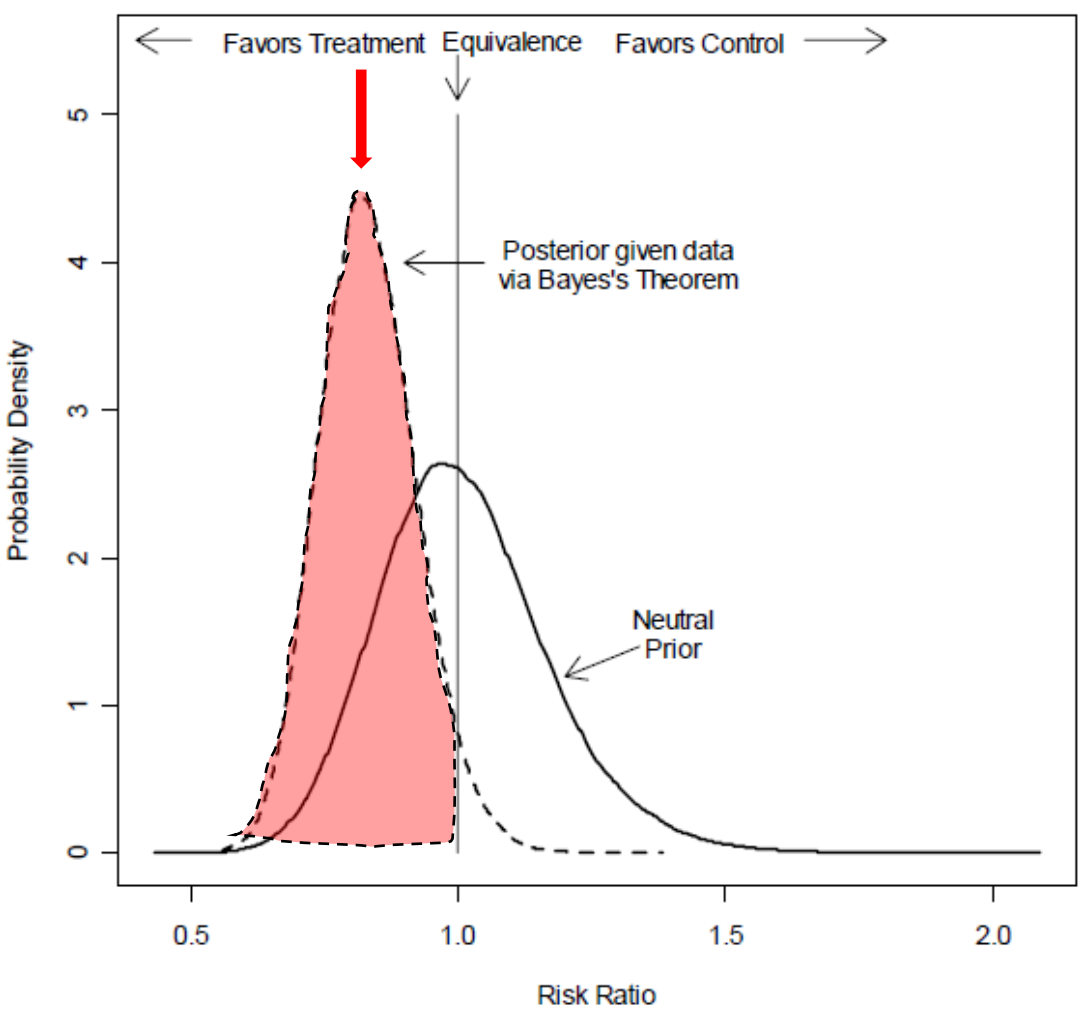
Primary Outcome

- Death **or** disability (severe or moderate)
  - Severe disability: **any** of Bayley III cognitive score <70, Gross Motor Function (GMF) 3-5, blindness, or hearing loss despite amplification
  - Moderate disability: Bayley III cognitive score 70-84 **and** any of GMF 2, seizure disorder, or hearing loss corrected with amplification
- Assessment targeted for 18-22 months
- Trained, certified ~~e~~examiners blinded to group assignment performed assessments

Sample Size and Pre-specified Analyses

- Sample size, N=168, pre-defined
  - Largest feasible estimate of available patients
- Intention to treat
- Bayesian analysis pre-defined: probability that the hypothesis is true based on the observed data
- Analyses adjusted for level of encephalopathy and center

A Hypothetical Bayesian Analysis



Prior distribution

Observed data

Posterior distribution:

- Point estimate
- 95% credible intervals
- Probability of posterior treatment benefit or harm
  - Area under the curve which lies < RR 1.0 (benefit) or >1.0 (harm)

July 2015 – Sept 2020
Enrollment over 5.2 yr

436 infants assessed for eligibility

254 met exclusion criteria
14 lacked consent

168 enrolled and randomized (92% of 182 eligible)

88 cooled

- 3 lost to F/U
- 2 incomplete F/U
- 18 died
- 65 followed

83 analyzed for primary outcome-94%

80 non-cooled

- 2 withdrawn
- 7 lost to F/U
- 2 incomplete F/U
- 9 died
- 60 followed

69 analyzed for primary outcome-86%

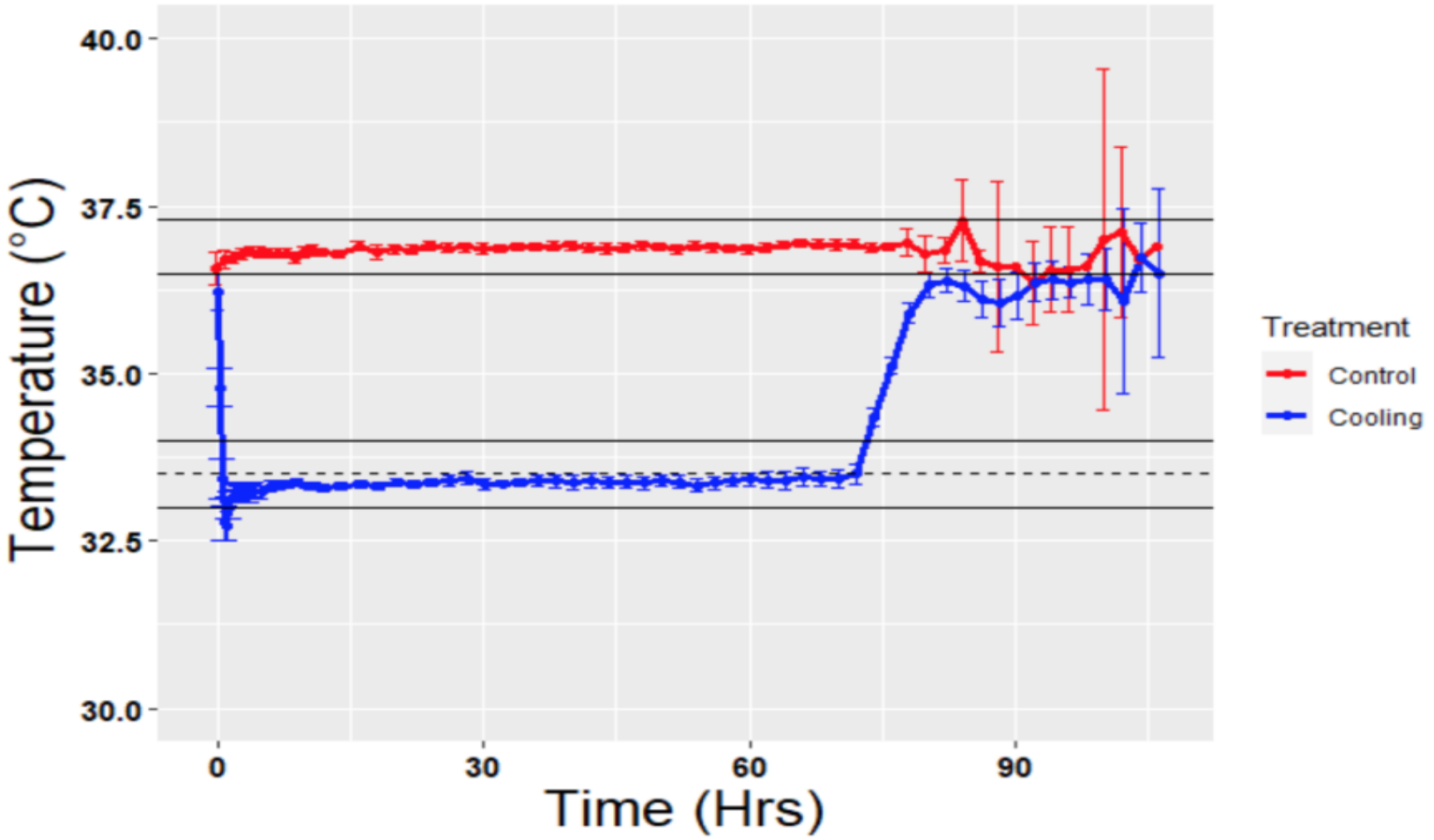
Maternal and Infant Characteristics

	Cooled (n=88)	Non-cooled (n=80)
	% or Mean ± SD	% or Mean ± SD
Maternal		
Fetal deceleration	**79**	**72**
Cord mishap	**10**	**9**
Placental problem	**44**	**46**
Emergent C-Section	**77**	**84**
Infant		
Gestational age - wk	**34.0 ± 0.8**	**34.1 ± 0.8**
Birth weight - gm	**2464 ± 634**	**2371 ± 608**
Male	**52**	**56**
Outborn	**53**	**59**

Maternal and Infant Characteristics

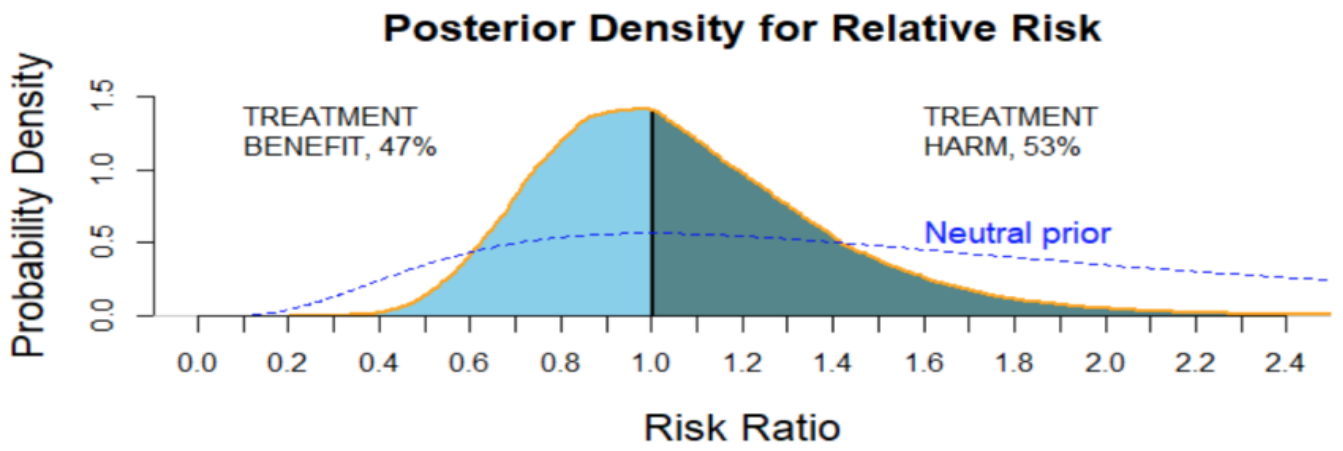
	Cooled (n=88)	Non-cooled (n=80)
	Mean ± sd or %	Mean ± sd or %
Delivery Room (DR)		
Intubation	**64**	**63**
Chest compressions	**46**	**38**
Epi-/other meds in DR	**30**	**33**
Apgars ≤ 5 at 10 min	**51**	**43**
pH, cord or BG <1 hr	**6.90 ± 0.20**	**6.90 ± 0.20**
Randomization		
Age in hrs	**4.5 ± 1.2**	**4.5 ± 1.3**
Moderate encephalopathy	**69**	**71**
Severe encephalopathy	**31**	**29**
Seizures alone	**0**	**0**

Mean Esophageal Temperature (Tes) Profiles



Posterior Probability of Death or Moderate/Severe Disability: Neutral Prior

	Cooled (n=83)		Non-cooled (n=69)		Bayesian results	
	#	%	#	%	aRR (95% credibility interval)	Probability of treatment harm*
Death or disability	29/83	**35**	20/69	**29**	**1.02 (0.58-1.82)**	**53%**



*Probability of treatment harm = Area under curve RR>1.0

Other Outcomes: Neutral Prior

Outcome	Cooled %	Non-Cooled %	aRR (95% CrI)	Prob of treatment harm
Death	21	13	1.30 (0.66-2.62)	**77%**
1° outcome with moderate encephalopathy	16	12	1.16 (0.54-2.54)	65%
1° outcome with severe encephalopathy	74	74	1.03 (0.76-1.47)	58%

*Probability of treatment harm = Area under curve RR>1.0

Safety Events

Event	Cooled, % (n=88)	Non-Cooled, % (n=80)	Posterior RR (95% CrI)
Major ICH	6	5	0.73 (0.28-1.84)
Thrombosis	0	0	-
Persistent acidosis	4	6	0.57 (0.22-1.40)
Major bleeding	1	5	0.39 (0.12-1.11)
Thrombocytopenia	11	13	0.77 (0.36-1.60)
Hyperglycemia	23	12	1.53 (0.80-2.97)
Hypoglycemia	1	6	**0.34 (0.11-0.94)**
PPHN	6	5	0.72 (0.27-1.81)
NEC	0	0	-

Conclusions

- Therapeutic hypothermia does **not** reduce the primary outcome of death or moderate/severe disability in infants born at 33^0 -35^6 weeks GA
- Therapeutic hypothermia may **increase** probability of death
- Except for hypoglycemia, there is no apparent difference for pre-specified safety events in cooled vs non-cooled groups

Neonatal Research Network Centers Recruitment/Follow-Up: 2015-2022

- Brown University
- Case Western Reserve University
- Children's Mercy Hospitals and Clinics, University of Missouri-Kansas City
- Cincinnati Children's Medical Center
- Duke University
- Emory University
- Nationwide Children's Hospital, Ohio State University
- RTI International
- Stanford University
- University of Alabama at Birmingham
- University of California – Los Angeles
- University of Iowa
- University of New Mexico
- University of Pennsylvania
- University of Rochester
- University of Texas Southwestern
- University of Texas Health Science Center-Houston
- University of Utah
- Wayne State University

Outcomes by GA

GA	Death or Moderate/Severe Disability %		Death %	
	Cooled	Control	Cooled	Control
33 wks	**41**	35	**16**	21
34 wks	**41**	31	**33**	6
35 wks	**24**	22	**17**	16