Up-to-date Systematic Review and Metaanalysis of Therapeutic Hypothermia for Neonatal Encephalopathy: Is the Crown Losing Its Sheen?

hypothermia (TH) holds the crown as the most effective intervention for neonatal hypoxic encephalopathy (HIE) [4]. The Cochrane review of 2013 had reported that TH reduces mortality [5], and this has been reiterated by another recent systematic review [6]. However, the latter has several methodological errors, including duplication of data from some trials, combining short-term and long-term mortality, as well as errors in data analysis [6]. In contrast to the findings of these, a systematic review, including trials exclusively from developing countries, did not find any benefit of TH on neonatal mortality [7]. More alarming, the HELIX trial [3],

The extensive critical appraisal [1,2] of the recently published HELIX trial [3] prompts this brief communication. Therapeutic

	Therapeutic hypothermia		Normothermia		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Aker 2019	2	25	5	25	2.0%	0.40 [0.09, 1.87]	
Akisu 2003	0	11	2	10	1.1%	0.18 [0.01, 3.41]	• · · · · · · · · · · · · · · · · · · ·
Bhardwaj 2012	3	62	6	62	2.4%	0.50 [0.13, 1.91]	
Bhat 2006	3	20	5	15	2.3%	0.45 [0.13, 1.59]	
Catherine 2020	22	78	29	84	11.3%	0.82 [0.52, 1.29]	
Chen 2018	0	18	1	18	0.6%	0.33 [0.01, 7.68]	· · · · · · · · · · · · · · · · · · ·
Elcher 2005	10	32	14	33	5.6%	0.74 [0.38, 1.41]	
Field 2013	8	56	4	55	1.6%	1.96 [0.63, 6.15]	· · · · · · · · · · · · · · · · · · ·
Jacobs 2011	13	110	19	110	7.7%	0.68 [0.36, 1.32]	
Joy 2012	1	58	4	58	1.6%	0.25 [0.03, 2.17]	
Lin 2006	2	32	2	30	0.8%	0.94 [0.14, 6.24]	
Perrone 2010	1	10	3	11	1.2%	0.37 [0.05, 2.98]	
Rakesh 2017	9	60	16	60	6.5%	0.56 [0.27, 1.17]	
Robertson 2008	7	21	1	15	0.5%	5.00 [0.69, 36.50]	
Shankaran 2002	2	9	3	10	1.1%	0.74 [0.16, 3.48]	· · · · · ·
Shankaran 2005	19	102	29	106	11.5%	0.68 [0.41, 1.13]	
Shimi 2014	4	10	8	10	3.2%	0.50 [0.22, 1.14]	
Simbruner 2010	5	62	13	63	5.2%	0.39 [0.15, 1.03]	
Sun 2012	0	23	1	28	0.5%	0.40 [0.02, 9.44]	· · · · · · · · · · · · · · · · · · ·
Tankgasalam 2015	16	60	30	60	12.1%	0.53 [0.33, 0.87]	
Thayyil 2013	4	17	2	16	0.8%	1.88 [0.40, 8.90]	
Thayyil 2021	72	202	49	206	19.6%	1.50 [1.10, 2.04]	
Yang 2020	1	33	2	30	0.8%	0.45 [0.04, 4.76]	· · · · · · · · · · · · · · · · · · ·
Total (95% CI)		1111		1115	100.0%	0.83 [0.71, 0.98]	•
Total events	204		248				
Heterogeneity: Chi2 =	35.60, df = 22 (P =						
Test for overall effect:	Z = 2.27 (P = 0.02	Favours (experimental) Favours (control)					

Panel A: Therapeutic hypothermia vs Normothermia for neonatal encephalopathy: Mortality before discharge

	Therapeutic hypothermia		Normothermia		Risk Ratio		Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
Azzopardi 2009	42	163	44	162	13.6%	0.95 [0.66, 1.36]			
Battin 2001	0	7	3	15	0.7%	0.29 [0.02, 4.89]			
Catherine 2020	22	76	29	79	8.7%	0.79 [0.50, 1.24]			
Field 2013	9	56	5	55	1.6%	1.77 [0.63, 4.94]			
Gluckman 2005	36	108	42	110	12.8%	0.87 [0.61, 1.25]			
acobs 2011	27	108	42	109	12.9%	0.65 [0.43, 0.97]			
□ 2009	1	38	3	44	0.9%	0.39 [0.04, 3.56]			
Shankaran 2005	24	102	38	106	11.5%	0.66 [0.43, 1.01]			
Simbruner 2010	20	53	33	58	9.7%	0.66 [0.44, 1.00]			
Thayyil 2021	84	198	63	201	19.2%	1.35 [1.04, 1.76]			
Zhou 2010	20	100	27	94	8.6%	0.70 [0.42, 1.15]			
Total (95% CI)		1009		1033	100.0%	0.88 [0.78, 1.01]		•	
Total events	285		329					2.5	
Heterogeneity: $Cht^2 = 20.30$, $df = 10$ (P = 0.03); $t^2 = 51\%$									10 100
Test for overall effect: Z = 1.83 (P = 0.07)								L nerimentall Favours (co	ntroll

Panel B: Therapeutic hypothermia vs Normothermia for neonatal encephalopathy: Mortality at 18-24 months of age

Fig. 1 Meta-analyses of therapeutic hypothermia vs normothermia for neonatal hypoxic encephalopathy, for short-term and long-term outcomes.

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	Therapeutic hypothermia		Normothermia		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M–H, Fixed, 95% CI	
Azzopardi 2009	74	163	86	162	15.9%	0.86 [0.68, 1.07]		
Battin 2001	2	7	4	15	0.5%	1.07 [0.25, 4.53]		
Catherine 2020	27	76	46	79	6.3%	0.61 [0.43, 0.87]		
Gluckman 2005	59	108	73	110	13.3%	0.82 [0.66, 1.02]		
Jacobs 2011	55	107	67	101	12.7%	0.77 [0.62, 0.98]		
LI 2009	7	38	21	44	3.6%	0.39 [0.18, 0.81]		
Shankaran 2005	45	102	64	106	11.5%	0.73 [0.56, 0.95]		
Simbruner 2010	27	53	48	58	8.4%	0.62 [0.46, 0.82]	_ 	
Thayyil 2021	96	195	94	199	17.1%	1.06 [0.87, 1.30]		
Zhou 2010	31	100	46	94	6.7%	0.63 [0.44, 0.91]		
Total (95% CI)		949		968	100.0%	0.79 [0.72, 0.86]	•	
Total events	425		549					
Heterogeneity: Chi ² =	19.44, df = 9 (P = 0	-						
Test for overall effect:	Z = 5.29 (P < 0.000	Eavours [experimental] Eavours [control]						
Test for overall effect:	Z = 5.29 (P < 0.000	0.2 0.5 1 2 5 Favours [experimental] Favours [control]						

Panel C: Therapeutic hypothermia vs Normothermia for neonatal encephalopathy: Mortality or disability at 18-24 months of age



Panel D: Therapeutic hypothermia vs Normothermia for neonatal encephalopathy: Disability at 18-24 months of age

	Therapeutic hypothermia		Normothermia		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	
Azzopardi 2009	33	120	48	117	30.9%	0.67 [0.47, 0.96]	-8-	
Field 2013	7	47	3	46	1.9%	2.38 [0.66, 8.67]		
Jacobs 2011	21	79	17	59	12.4%	0.92 [0.54, 1.59]		
LI 2009	2	37	6	41	4.6%	0.28 [0.06, 1.22]		
Shankaran 2005	15	77	19	64	13.2%	0.66 [0.36, 1.18]	_ - +	
Simbruner 2010	4	32	10	21	7.7%	0.26 [0.09, 0.73]		
Thayyii 2021	12	111	28	136	16.0%	0.53 [0.28, 0.98]		
Zhou 2010	10	60	19	67	13.1%	0.44 [0.22, 0.88]		
Total (95% CI)		583		553	100.0%	0.63 [0.50, 0.78]	•	
Total events	104		152					
Heterogeneity: Chi ² =	11.45, $df = 7 (P = 0)$	1.12); ¹² =	39%					100
Test for overall effect: Z = 4.17 (P < 0.0001)							Favours [experimental] Favours [control]	100

Panel E: Therapeutic hypothermia vs Normothermia for neonatal encephalopathy: Cerebral palsy at 18-24 months of age

reported increased short-term and long-term mortality, in low and middle income country settings. Such divergent results necessitate an up-to-date systematic review to evaluate the effect of therapeutic hypothermia (inter-vention) versus normothermia (comparison) in neonatal hypoxic encephalopathy (population), on mortality and neuro-development (outcomes).

We searched multiple databases without language or date restrictions, published up to 30 September, 2021. We included randomized controlled trials (RCT) comparing therapeutic hypothermia (defined as whole-body or selective head cooling, to temperature <34.5 °C for 48-72 hours) initiated within 6 hours of birth, versus no hypothermia, in neonates with hypoxic encephalopathy (defined by Apgar scoring and/or cord blood analysis, and supportive clinical findings), and reporting any of the following outcomes: mortality before discharge, mortality at 18-24 months, mortality or neurologic disability at 18-24 months, disability at 18-24 months, and cerebral palsy at 18-24 months.

We identified 36345 citations, of which 149 citations were

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short-listed, and 32 publications (reporting 29 trials), were included. Using Cochrane Risk of Bias (RoB) 2 tool [8], two authors independently categorized, 11, 8, and 10 RCT as having high, moderate, and low RoB. Meta-analysis using Cochrane Review Manager [9] (fixed effect model) [10] revealed pooled relative risks (95% CI) as follows (**Fig. 1**): Mortality before discharge: 0.83 (0.71, 0.98), 23 trials, 2221 participants, I^2 38%; mortality at 18-24 months: 0.88 (0.78, 1.01), 11 trials, 2042 participants, I^2 51%; mortality or neurologic disability at 18-24 months: 0.79 (0.72, 0.86), 10 trials, 1914 participants, I^2 54%; neurologic disability at 18-24 months: 0.63 (0.53, 0.75), 10 trials, 1327 participants, I^2 37%; and, cerebral palsy at 18-24 months: 0.63 (0.50, 0.78), 8 trials, 1136 participants, I^2 39%. These data suggested statistically significant benefit for all outcomes except mortality at 18-24 months of age.

Subgroup analysis by study setting (developed versus developing countries) showed marked differences in mortality before discharge: RR 0.68 (95% CI 0.51, 0.92), 8 trials, 790 participants, I^2 0% versus RR 0.91 (95% CI 0.75, 1.10), 15 trials, 1431 participants, I^2 49%; and mortality at 18-24 month: RR 0.79 (0.66, 0.93), 7 trials, 1212 participants, I^2 7%, versus RR 1.05 (0.86, 1.29), 4 trials, 830 participants, I^2 65%. Other outcomes showed benefit of TH in both developed and developing countries, the magnitude of effect being greater in developing countries for disability and cerebral palsy.

The respective risk ratios (95% CI) for trials with low versus moderate/high RoB were as follows: Mortality before discharge: 1.04 (0.84, 1.29), 7 trials, 1186 partici-pants, I² 62%, versus 0.63 (0.49, 0.80), 16 trials, 1035 participants, I² 0%; mortality at 18-24 months: 0.97 (0.82, 1.15), 5 trials, 1011 participants, I² 60%, versus 0.78 (0.64, 0.96), 6 trials, 1031 participants, I² 7%; mortality or neurologic disability at 18-24 months: 0.86 (0.76, 0.97), 5 trials, 997 participants, I² 55%, versus 0.71 (0.62, 0.81), 5 trials, 920 participants, I² 40%; neurologic disability at 18-24 months: 0.56 (0.54, 0.82), 5 trials, 734 participants, I² 40%, versus 0.58 (0.43, 0.78), 5 trials, 593 participants, I² 41%; and, cerebral palsy at 18-24 months: 0.70 (0.46, 1.05), 2 trials, 385 participants, I² 44%, versus 0.60 (0.46, 0.78), 6 trials, 751 participants, I² 45%.

These data confirm that some of the benefits of TH reported in trials and systematic reviews are biased by studies with moderate/high RoB. TH reduces neurologic disability and cerebral palsy in later infancy in diverse settings. However, the expected benefit on short-term and long-term mortality is uncertain, especially in developing country settings. A systematic review with several additional outcomes is in progress (PROSPERO 2021 CRD42021279682). Meanwhile, these findings will help physicians, families, and policymakers, to make evidenceinformed choices and decisions about therapeutic hypothermia for neonatal encephalopathy.

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JOSEPH L MATHEW,^{1*} NAVNEET KAUR,¹ JEANNE M DSOUZA² From ¹Department of Pediatrics, Advanced Pediatrics Centre, Postgraduate Institute of Medical Education and Research, Chandigarh; ²Kasturba Medical College, Manipal, Karnataka. *dr.joseph.l.mathew@gmail.com

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