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ARTICLE

Characteristics and short-term outcomes of neonates with mild hypoxic-ischemic encephalopathy treated with hypothermia

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Abstract

Objective To compare the characteristics and outcomes of neonates with mild hypoxic-ischemic encephalopathy (HIE) who received hypothermia versus standard care.

Study design We conducted a retrospective cohort study of neonates ≥35 weeks' gestation and ≥1800 g admitted with a diagnosis of Sarnat stage 1 encephalopathy. We evaluated length of hospital stay, duration of ventilation, evidence of brain injury on MRI, and neonatal morbidities.

Results Of 1089 eligible neonates, 393 (36%) received hypothermia and 595 (55%) had neuroimaging. The hypothermia group was more likely to be outborn, born via C-section, had lower Apgar scores, and required extensive resuscitation. They had longer durations of stay (9 vs. 6 days, $P < 0.001$), respiratory support (3 vs. 2 days, $P < 0.001$), but lower odds of brain injury on MRI (adjusted odds ratio 0.33, 95% CI: 0.22–0.52) compared with standard care group.

Conclusion Despite prolongation of hospital stay, hypothermia may be potentially beneficial in neonates with mild HIE; however, selection bias cannot be ruled out.

Introduction

Hypoxic-ischemic encephalopathy (HIE) in neonates is a significant healthcare burden due to adverse neurodevelopmental outcomes with lifelong consequences [1]. A proportion of brain injury in HIE occurs as a result of primary hypoxic-ischemic insult; however, the majority of postasphyxial brain injury occurs during a secondary phase, after reestablishment of cerebral circulation and oxygenation. This has led to the development and use of neuroprotective strategies such as therapeutic hypothermia (TH) aimed at reducing secondary neuronal injury [2]. Hypothermia attenuates the neuronal apoptotic pathway if initiated within 6 h of birth and continued for 72 h [3–5]. Following successful translation from preclinical models, hypothermia has been shown to be safe and effective in neonates with moderate to severe HIE [6–8].

TH is not a benign intervention. It predisposes neonates to side effects such as cardiac arrhythmias, thrombocytopenia, coagulopathy, and subcutaneous fat necrosis [9]. Moreover, TH leads to mother–infant separation, intensive care monitoring, invasive procedures, and often sedation to reduce stress. Based on the evidence from randomized controlled trials, the current recommendation is to limit use

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of TH to neonates with moderate to severe HIE, in keeping with the studied populations. However, in practice, often TH is offered to neonates with mild HIE, due to difficulty in early clinical assessment of the severity of encephalopathy and the need to initiate treatment within 6 h of age. A major reason for targeting moderate–severe HIE neonates only in the hypothermia trials was based on previous reports of similar psychoeducational scores in neonates with mild encephalopathy compared with their peers [10]. It has been increasingly recognized that earlier reports may have potentially underestimated the problem, since reports of marginally lower cognitive scores in all domains at 5 years in mild HIE neonates compared with controls were published [11]. Mild HIE infants had higher rate of intact survival but on detailed neuropsychological and behavorial assessment performed no better than children with moderate HIE [11, 12]. More recently El-Dib et al. suggested redefining the traditionally accepted cut off for defining poor neurological outcome in mild HIE infants [13]. Accordingly they reanalyzed the results from a prospective multicenter study (PRIME study) and found that 16 and 23% of neonates with mild encephalopathy had cognitive scores ≤85 and ≤90, respectively, while almost 40 and 56% of infants had at least one cognitive, motor, or language score of ≤85 and ≤90 respectively [13]. Our objective was to evaluate the characteristics and short-term outcomes of neonates presenting with mild HIE at initial assessment who received or did not receive TH in a multicenter national cohort.

Patients and methods

Design and participants

We conducted a retrospective cohort study using data from the Canadian Neonatal Network (CNN), which captures data from >95% of neonates admitted to tertiary neonatal intensive care units (NICUs) in Canada. Data were abstracted from neonatal medical records by trained personnel according to standardized definitions and transmitted to the CNN Coordinating Centre at the Maternal-infant Care Research Centre in Toronto, Ontario, as previously described [14]. The data collected by CNN have been shown to be highly reliable and consistent [15]. Neonates born at ≥35 weeks of gestation with a birth weight of >1800 g admitted with the diagnosis of mild HIE (Sarnat stage 1 encephalopathy) [16] to participating NICUs between January 2010 and December 2017 were included. Neonates who had moderate or severe encephalopathy, congenital neuromuscular disease, or major congenital or chromosomal anomalies, or who were missing data on TH/encephalopathy staging were excluded.

Variable definitions

Receipt of chest compression and/or epinephrine was considered extensive resuscitation. The stage of encephalopathy at admission was collected and neonates were categorized accordingly: (i) Encephalopathy: the grade at admission was used to classify neonates as mild, moderate, or severe according to Sarnat and Sarnat staging criteria [16]. (ii) No encephalopathy: does not meet entry criteria of HIE, or meets some criteria for hypoxic-ischemic event but has no evidence of encephalopathy; (iii) Not available: death before a diagnosis or data are unavailable; (iv) Unknown stage: meets entry criteria for HIE but data on staging cannot be ascertained from charts or does not meet entry criteria for HIE but TH initiated. The specific time of diagnosis was not collected in our database, therefore this data was not available. Charts were reviewed for occurrence of seizures at any time during NICU stay and ascribed as follows: (i) Definite seizure: witnessed by >2 clinicians or diagnosed by electroencephalogram (EEG) or one clinical observation of seizure-like movements coupled with administration of antiepileptic; (ii) Suspected seizure: observed by only one clinician or movements of uncertain significance not accompanied by a diagnosis of seizures or administration of antiepileptic; and (iii) No seizure: absence of seizures or seizure-like movements. Among the neonates who received TH, time of initiation, time to reach target temperature, time of rewarming, and total duration of hypothermia were recorded.

Adverse events during the receipt of TH were recorded according to the following definitions: (i) Hypotension treated using fluids or inotropes; (ii) Thrombocytopenia treated using platelet transfusion; (iii) Coagulopathy treated using fresh frozen plasma, blood transfusion, or cryoprecipitate; (iv) Persistent metabolic acidosis, defined as pH < 7.0 on two consecutive samples obtained at least 6 h apart after initiation of TH. These complications may also be secondary to the effects of HIE and we could not distinguish them completely. End-organ dysfunction was recorded according to the following definitions: (i) Persistent pulmonary hypertension (PPHN), echocardiographic, or clinical diagnosis; (ii) Renal failure, defined as urine output <0.5 ml/kg/h or rising creatinine >100 mmol/l at any time within the first 72 h of birth; (iii) Disseminated intravascular coagulation, defined as laboratory and clinical evidence of coagulopathy; (iv) Hepatic dysfunction, defined as aspartate transaminase or alanine transaminase (ALT) > 100 IU; (v) Cardiac dysfunction, defined as the receipt of inotrope or echocardiographic evidence of cardiac dysfunction.

Outcomes

We evaluated the outcomes of duration of hospital stay in tertiary care NICU, duration of any respiratory support (invasive or noninvasive), and magnetic resonance imaging

(MRI) evidence of brain injury. Evidence of brain injury was defined as signal abnormalities in MRI sequences (T1-weighted or T2-weighted or diffusion-weighted imaging) in any of the following patterns: (i) Watershed pattern: located on the border of the vascular territories—parasagittally, including the cerebral cortex and the subcortical white matter; (ii) Deep gray matter pattern: may include basal ganglia, thalamus, posterior limb of internal capsule, hippocampi, dorsal brainstem, perirolandic cortex, or subcortical tissues; and (iii) Mixed pattern: presence of a combination of the above patterns.

Research ethics

The data collection and analysis methods for this study were approved by the The Hospital for Sick Children Research Ethics Board.

Statistical analyses

Neonatal characteristics and clinical outcomes of the hypothermic and normothermic neonates were compared using the Pearson's χ^2 test for categorical variables and the Student's t test or Mann–Whitney U test for continuous variables. The effects of infant characteristics, including gestational age, Apgar score <5 at 5 min, receipt of extensive resuscitation (chest compression and/or epinephrine), being outborn, delivery by cesarean section, and treatment with TH, on MRI evidence of brain injury were investigated in logistic regression models. The effect of each variable was also adjusted for those of all other variables in the logistic regression models. Statistical analyses were conducted by using SAS V.9.3 (SAS Institute, Cary, North Carolina, USA), and a P value of <0.05 was considered significant.

Results

Of the 3715 term and near term neonates who were admitted with HIE, 1089 neonates (29.3%) were classified as mild HIE and were included in the study cohort (Fig. 1) of whom 393 (36%) received TH. Compared with the standard care group, more neonates in the TH group were outborn, delivered by cesarean section, and received mechanical ventilation (Table 1). The latter also had higher rates of receiving extensive resuscitation and lower Apgar scores at 5 min. Although the neonates in the TH group were born at a lower gestational age, the mean difference was not clinically significant. The number of neonates with mild HIE and the proportion of them receiving TH has increased significantly over time, from 28% in 2010 to 45% in 2017 (Cochran-Armitage trend test $P = 0.023$) (Fig. 2). Median (IQR) time of initiation of hypothermia was 3.6 h (1.8–5.3 h) after birth, whereas time to reach target temperature was 5.9 h (4.1–7.9 h) after birth. Mean (SD) of maximum and minimum temperatures recorded during TH was 34.4 °C (0.7 °C) and 32.8 °C (0.8 °C), respectively. The majority of neonates received TH for 72 h, with a median (IQR) time to complete rewarming around 76 h (73.5–77.7 h) of age. Thirty-one percent of neonates who were started on TH had earlier termination of TH (before 72 h). We did not collect data on the reasons for stopping TH.

Compared with the standard care group, the TH group had a significantly longer length of stay in a tertiary care NICU (median [IQR] 9 days [7–12 days] vs. 6 days

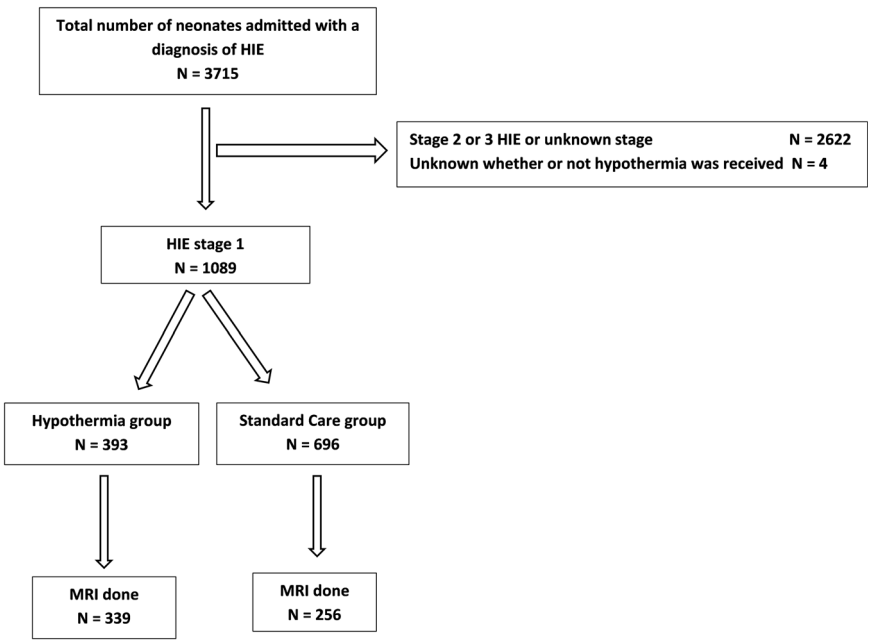

Fig. 1 Flow diagram of the study population. HIE hypoxic-ischemic encephalopathy, MRI magnetic resonance imaging

Table 1 Clinical characteristics and outcomes of the cohort

Variables	Hypothermia group ($N = 393$)	Standard care group ($N = 696$)	P value
Male sex[a]	239 (61%)	419 (60%)	0.84
Gestational age in weeks	38.9 (1.7)	39.1 (1.6)	0.05
Birth weight in grams	3300 (562)	3359 (587)	0.11
Outborn[a]	292 (74%)	400 (57%)	<0.01
Vaginal birth[a]	201 (51%)	402 (58%)	0.03
Gestational diabetes[a]	45 (12%)	90 (13%)	0.46
Maternal hypertension[a]	49 (13%)	76 (11%)	0.43
Resuscitation[a]			<0.01
Minimal (none, suction, stimulation, or free flow oxygen)	12 (3%)	67 (10%)	
Moderate support (CPAP/PPV with bag-mask or intubation)	285 (73%)	531 (76%)	
Extensive (chest compression and/ or epinephrine)	94 (24%)	90 (13%)	
Missing information	2 (1%)	8 (1%)	
Need for mechanical ventilation at anytime[a]	195 (50%)	200 (29%)	<0.01
Apgar score at 5 min <5[a]	208 (54%)	239 (35%)	<0.01
Apgar score at 5 min, median (IQR)	4 (3, 6)	5 (4, 7)	<0.01
Apgar score at 10 min <5[a]	95 (27%)	67 (11%)	<0.01
Apgar score at 10 min, median (IQR)	6 (4, 7)	7 (6, 8)	<0.01
Received opioid infusion[a]	264 (67%)	86 (12%)	<0.01
Length of hospital admission (days)[b]	9 (7–12)	6 (4–9)	<0.01
Duration of any respiratory support (days)[b]	2 (0–5)	1 (0–2)	<0.01
Duration of invasive respiratory support (days)[b]	0 (0–2)	0 (0–1)	<0.01
Gavage feeding at discharge from level III NICU[a]	88 (22%)	89 (13%)	<0.01
Persistent pulmonary hypertension[a]	43 (11%)	46 (7%)	0.01
Renal failure[a]	52 (13%)	56 (8%)	<0.01
Disseminated intravascular coagulation[a]	33 (8%)	12 (2%)	<0.01
Hepatic dysfunction[a]	89 (23%)	74 (11%)	<0.01
Cardiac dysfunction[a]	32 (8%)	17 (2%)	<0.01
Seizure at any time during admission[a]	69 (18%)	141 (20%)	0.28

CPAP continuous positive airway pressure, *IQR* interquartile range, *NICU* neonatal intensive care unit, *PPV* positive pressure ventilation

[a]*n* (%) for categorical variables

[b]Median (IQR) for continuous variables

[4–9 days]; $P < 0.01$), along with a prolonged duration of respiratory support (Table 1). Table 1 also summarizes the systemic comorbidities associated with mild HIE in the two groups: Neonates exposed to TH were more likely to have received opioid infusions compared with those not exposed to TH. Adverse events which might be related to TH were recorded only for those who received TH ($N = 393$), and were as follows: hypotension in 60 (16%), thrombocytopenia in 36 (10%), coagulopathy in 63 (17%), and persistent metabolic acidosis in 28 (8%).

Brain MRI was completed in 595 (55%) of the neonates in the study cohort: 339/393 neonates (86%) in the hypothermia group and 256/696 neonates (37%) in the standard care group (Table 2). The difference between the clinical characteristics of neonates who had MRI compared with those who did not have MRI in the hypothermia group were not statistically significant (Supplementary Table 1). On the other hand, subcohort comparison of neonates who received standard care, revealed that those who had MRI were more likely to be outborn, have received extensive resuscitation, and have been born by C-section (Supplementary Table 2) compared with those who did not have MRI. Of those who had neuroimaging, 59% of neonates in the TH group and 38% neonates in the standard care group had no MRI evidence of brain injury (Table 2). We excluded from multivariable analyses the neonates who did not have a clear description of pattern of brain injury, usually associated with HIE, leaving 439/595 neonates (74% of total) available for neuroimaging-related brain injury evaluations (Table 2). In multivariable analyses adjusted for the effects of several

clinical variables, higher gestational age and TH treatment were associated with lower odds of having an abnormal MRI (Table 3).

Discussion

In this national cohort study, we identified that the proportion of neonates with mild HIE who received TH in Canada has increased steadily over years of the study period. Neonates who were delivered by cesarean section, at a community hospital, with lower Apgar scores at 5 min of age, or received extensive resuscitation and needed mechanical ventilation were more likely to have received TH intervention. Receipt of TH following mild HIE was associated with significantly longer stays, longer durations of respiratory support, but lower odds of brain injury on imaging.

Studies from other countries have shown similar trends in clinical practice in the management of mild HIE. Kracer et al. and Massaro et al. reported from a US perinatal database that 50–75% of neonates with mild HIE were treated with hypothermia, with an increasing trend over time [17, 18]. Gagne-Loranger et al. reported that, among the neonates referred to a tertiary care NICU for TH, 36% (79/215) had mild encephalopathy, of whom 16% (13/79) of neonates received TH [19]. Oliveira et al. concluded from a survey that 75% of cooling centers in the United Kingdom offered TH for neonates with mild encephalopathy, while 19% of these centers even considered initiating TH beyond 6 h of age, and 36% would discontinue TH prior to 72 h [20]. Depending upon the available resources, factors considered during the decision making included neurological examination with or without amplitude integrated EEG (aEEG) [20, 21]. Although most standardized protocols adopted their eligibility criteria based on the cooling trials, almost 40% of neonates enrolled in the Vermont Oxford Network Registry had neither moderate to severe encephalopathy nor seizures before initiation of TH [22]. A meta-analysis of 13 observational studies, mainly retrospective, including 2783 neonates, reported that 22% (95% CI 16–27%; range 9–54%) of neonates who underwent TH had mild HIE [23]. The authors also highlighted the fact that, except for one, all of the previous studies were designed primarily to study neonates with moderate to severe encephalopathy. Overall, there has been a slow therapeutic drift toward offering hypothermia to neonates with mild HIE. It is concerning that, in the absence of standardized decision making criteria, TH is being offered to neonates who may not completely meet the eligibility criteria for cooling and can lead to variability in practice.

We identified that the characteristics of neonates with mild HIE who received TH included outborn status, receipt of extensive resuscitation, and low Apgar scores. Our results are in concordance with the literature where similar risk factors have been identified [18, 23–26]. During the transport of such neonates, passive hypothermia is often initiated, while some centers have the resources to provide active hypothermia on transport (ice packs or servo-

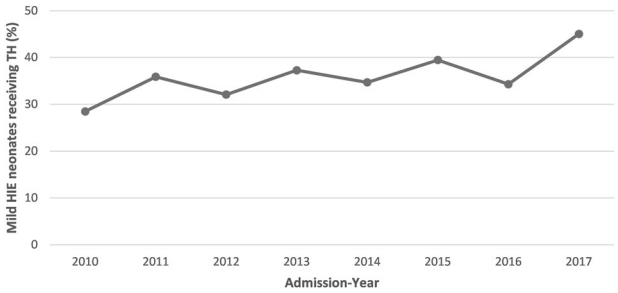

Fig. 2 Time trend analysis of neonates admitted with diagnosis of hypoxic-ischemic encephalopathy who received hypothermia. HIE hypoxic-ischemic encephalopathy, TH therapeutic hypothermia

Table 2 MRI brain abnormalities of neonates with mild hypoxic-ischemic encephalopathy

MRI brain abnormalities ($N = 595$)	Hypothermia group ($N = 339$)	Standard care group ($N = 256$)	P value
Normal, n (%)	199 (59%)	98 (38%)	<0.01
Watershed pattern/white matter injury only, n (%)	19 (6%)	34 (13%)	0.01
Basal ganglia/thalamic pattern injury only, n (%)	16 (5%)	13 (5%)	0.84
Mixed watershed and basal ganglia pattern of injury, n (%)	2 (0.6%)	2 (0.8%)	1.00
Ancillary findings			
Focal restricted diffusion changes not conforming to specific pattern, n (%)	0	2 (0.8%)	0.18
Hemorrhage, n (%)[a]	50 (15%)	40 (16%)	0.76
Pattern of injury not well defined, n (%)[a]	78 (23%)	72 (28%)	0.15

The injury patterns are not mutually exclusive

MRI magnetic resonance imaging

[a]These categories were not included in the definition of abnormal MRI findings

Table 3 Effect of clinical variables on abnormal MRI outcomes of neonates with mild hypoxic-ischemic encephalopathy

Variables	Univariate analysis		Adjusted[a] multivariable analysis	
	OR	95% CI	OR	95% CI
Gestational age (weeks)	0.84	(0.75, 0.95)	0.83	(0.74, 0.95)[b]
Apgar score at 5 min <5	0.56	(0.37, 0.85)	0.72	(0.45, 1.16)
Need for extensive resuscitation	0.87	(0.52, 1.44)	1.13	(0.63, 2.04)
Outborn	0.75	(0.48, 1.17)	0.75	(0.46, 1.21)
Cesarean section	1.02	(0.68, 1.52)	0.97	(0.63, 1.49)
Receipt of therapeutic hypothermia	0.33	(0.22, 0.49)	0.33	(0.21, 0.51)[b]

Abnormal MRI was defined as any MRI that showed abnormal signals on conventional and/or diffusion-weighted imaging in the watershed distribution and/or deep gray matter

CI confidence interval, *OR* odds ratio

[a]The effect of each clinical variable was adjusted for the effects of the five other variables in the table

[b]Statistically significant

controlled cooling devices) [18]. Clinicians also use markers of perinatal acidemia, for which we did not have data available, in decision-making for TH. Similar to other database studies, limitations of the database meant that we were unable to characterize all the nuances of medical decision-making regarding the initiation of TH. It is likely that outborn infants were more often treated with TH due to the potentially several possibilities. These include difficulty in monitoring these neonates in community hospitals, time constraints with need to initiate TH within first 6 h and possibility of neonates with higher severity of illness making selection bias a true possibility.

Current standardized protocols for TH are resource-intensive and include admission to a tertiary intensive care, invasive procedures, and separation of the mother–infant dyad. Maintaining subphysiological temperatures have been associated with adverse effects, including inadvertent extreme hypothermia (32%), bradycardia (100%), PPHN (6–22%), hyperglycemia (11%), subcutaneous fat necrosis (2%), thrombocytopenia (8–41%), and coagulopathy (19%), in previous retrospective studies of neonates with mild HIE [23]. The incidence of adverse effects in our cohort was in keeping with previous reports, underscoring the need to consider the risks versus benefits of TH in individual patients. Most of these complications are transient and the perinatal hypoxic insult may in itself contribute to or be causing such complications.

A few reports of outcomes following TH in mild HIE exist without consistent results. In a single centre study of 215 neonates with perinatal depression, normothermic neonates (40%) had higher frequencies of brain injury than patients who received TH (31%) [19]. Walsh et al. reported that 23% of neonates with mild HIE who received TH had features of moderate to severe brain injury on MRI [27]. Dupont et al. found that 20% (12/60) of normothermic neonates with mild encephalopathy had at least one abnormal short-term outcome, including the presence of seizures, abnormal neurological examination at discharge, or feeding difficulties beyond the first week of life. Five neonates in their cohort developed seizures between 12 and 40 h of age, indicating evolution in the stage of encephalopathy. Brain MRIs were performed in only a small group (11%) of the neonates, and the majority were abnormal [24]. The Children's Hospital Neonatal Consortium Database reported that 41% (53/132) of neonates with mild HIE who received TH had normal MRI, 10% had clinical seizures, and 17% had electrographic seizures [18]. In the PRIME study, which recruited neonates with mild HIE based on a rigorous definition (evidence of significant perinatal acidosis and/or a hypoxic-ischemic event with need for resuscitation, but neurological examination insufficient to meet cooling criteria), 17% of their study cohort had abnormal pattern of MRI changes [28]. On the contrary, another prospective multicenter cohort study (MARBLE), which recruited consecutive term and near-term neonates with neonatal encephalopathy who received TH, reported that out of 37 neonates with mild HIE, one infant developed cerebral palsy, while 20 had mild to moderate white matter injury [29]. In comparison to the PRIME study, we found a higher rate of gavage feeding at discharge (0 vs. 13%), seizures (2 vs. 20%), and abnormal MRI (17 vs. 62%) among neonates who received standard care. The differences in our results can be explained by the strict inclusion criteria in PRIME study to maintain consistency of neurological examinations between centers versus the lack of standardized neurological examination in our study.

Though our results indicate that those who received TH had less evidence of brain injury on MRI despite being more clinically affected initially by the asphyxial event, we would like to recognize that we cannot rule out selection bias. Neonates who received TH had several characteristics different from those who did not receive TH, and there was a likelihood of selection bias in those who had MRI evaluation. Therefore, despite the apparent benefit of TH, we strongly suggest that TH should be evaluated in a randomized trial for neonates with mild HIE before adoption as a routine therapy.

Hypothermia therapy is no doubt resource-intensive, further stressing the need for risk stratification for optimal allocation of resources to the neonates who are most likely to benefit. A major limitation to this process is the accuracy of neurological examination to judge eligibility at initiation of therapy. Neonatal hypoxic-ischemic injury is a dynamic process that evolves over the first few days of life [16, 30].

The reliability of early neurological examination has been questioned, with the appreciation that TH may also attenuate the severity of encephalopathy over the first few hours [13, 24, 25]. Tools such as aEEG, near-infrared spectroscopy, and heart rate variability may be helpful in the future for early optimal patient selection. Recently, the Neonatal Neurocritical Care Special Interest Group [13] proposed a framework for pragmatic clinical trials that can aim to differentiate neonates at high risk of disability from those who are truly "mildly" affected, by two approaches: either by broadening the previous cooling eligibility criteria to include signs of less severe encephalopathy or extending the acidosis inclusion criteria to include complementary biomarkers. While there is consensus on the need for RCT, there is disagreement upon the inclusion criteria [13]. Video recording the neurological examination for later review for standardized interpretation accross sites and objective scoring system embedded within the Sarnat staging has been recently proposed [13, 31]. Several molecular biomarkers of neurological injury, oxidative stress, metabolites, inflammatory markers may potentially help in early diagnosis and triaging, however, the sensitivity and specificity of these biomarker panels in mild HIE is yet to be validated in large cohorts [32]. Gagne-Loranger et al. demonstrated aEEG can be used as a tool for risk stratification. In a subcohort study they showed that 31% of mild HIE neonates with abnormal aEEG (and thus were cooled) had abnormal MRI, whereas all neonates with normal aEEG (and thus were not cooled) had no evidence of brain injury on MRI [19].

Although better screening tools are needed to identify the subcohort of mild HIE infants eligible to receive TH, we speculate whether individual tools are able to entirely characterize the substantial heterogeneity within this cohort. Multiple factors, such as mechanism of injury, timing of injury, antenatal environment, socioeconomic status, and variations in clinical practice may affect neurodevelopmental outcome. Standardized management protocols that minimize differences in regional practices will be necessary to make valid comparisons. Development of multidimensional data repositories, including clinical data, biomarkers data, neuroimaging, and outcome data may help facilitate collaborative research to precisely characterize mild HIE and improve the design of future clinical trials [33, 34].

Key strengths of our study include a large, population-representative sample of neonates with mild HIE admitted to tertiary NICUs and comprehensive neonatal information from a reliable database. However, our study also has limitations as a retrospective study, where classification of the severity of encephalopathy in this study cohort was based on admission neurological examination which was not standardized across centers. Recently, Chalak et al. demonstrated that more objective categorization of Sarnat scoring criteria may be able to classify neonates with higher encephalopathy burden and at risk of disability [32]. Such objective scoring of neurological examination may be included in future prospective trials. Second, only half of the cohort had MRI results available, and the clinical indication or timing of performing MRI in standard care neonates was not recorded. Although there was no difference between the subcohort of hypothermic neonates who had MRI results available versus those who did not, surprisingly a considerable proportion of mild HIE neonates who did not receive TH had MRI assessment during hospital admission. These neonates were more likely to be outborn, delivered by C-section and received extensive resuscitation indicating that they may have higher severity of illness. All MRI in the standard care group were done based on clinical team's decision. Among the small group of infants who received hypothermia and neuroimaging was not available, there could be infants who had earlier termination of cooling (reasons not available in database) and those who had missing results.Third, we only evaluated MRI-associated brian injury and not the results of neurodevelopmental assessments of the neonates. This was because follow-up of these neonates across the country is not routine. Most centers in Canada would not follow the mild HIE infants who did not receive cooling and only some centers would follow mild HIE infants who received cooling and had a normal MRI. Fourth, our cohort may be an underrepresentation of all neonates with mild HIE, as it is likely that more severely affected neonates are more readily identified at peripheral centers and referred to tertiary care. There is an element of subjectivity in the neurological assessment or assignment of an Apgar score. Supportive data on acidosis immediately following birth were not available. Thus, while the neonates in our study were all classified as 'mild', it is possible that those who were referred to the tertiary NICU were potentially sicker than those who were not referred; and that those who were cooled were sicker than those who were not cooled. The effect of such a selection bias due to confounding by indication cannot be ruled out without a randomized trial. Last, staging of the disease recorded in our database has been at variable hours of age. HIE being an evolving disease, the age of assessment is an important criterion, however this information is not captured by the database and needs to be addressed in future prospective studies.

Conclusion

In this large, multicenter, national cohort, treatment with TH following mild HIE in neonates was associated with longer stays, longer durations of respiratory support, but lower odds of brain injury on imaging compared with those not treated with TH; however, selection bias cannot be ruled out. The adverse effects of TH in neonates with mild HIE

are few, and timely initiation and optimal temperature management are achievable in most centers. Our results strongly underscore the need for well-designed trials to evaluate the neuroprotective efficacy of TH for mild HIE.

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Author contributions IRG conceptualized and designed the study, designed the data collection instruments, collected data, carried out the initial analyses, and drafted, reviewed, and revised the paper. HW reviewed the initial study proposal and research ethics application, contributed to the acquisition and interpretation of data, and reviewed and revised the paper. PW, KM, SS, and DL contributed to the interpretation of data and critically reviewed and revised the paper. EWY contributed to the analysis and interpretation of data and revised the paper. PSS conceptualized and designed the study, coordinated and supervised the data collection, and critically reviewed and revised the paper for important intellectual content. As corresponding author, PSS confirms that he has had full access to the data in the study and final responsibility for the decision to submit for publication.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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