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Early Glycemic State and Outcomes of Neonates With Hypoxic-Ischemic Encephalopathy

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abstract

OBJECTIVES: In infants with hypoxic-ischemic encephalopathy (HIE), conflicting information on the association between early glucose homeostasis and outcome exists. We characterized glycemic profiles in the first 12 hours after birth and their association with death and neurodevelopmental impairment (NDI) in neonates with moderate or severe HIE undergoing therapeutic hypothermia.

METHODS: This post hoc analysis of the High-dose Erythropoietin for Asphyxia and Encephalopathy trial included $n = 491$ neonates who had blood glucose (BG) values recorded within 12 hours of birth. Newborns were categorized based on their most extreme BG value. BG >200 mg/dL was defined as hyperglycemia, BG <50 mg/dL as hypoglycemia, and 50 to 200 mg/dL as euglycemia. Primary outcome was defined as death or any NDI at 22 to 36 months. We calculated odds ratios for death or NDI adjusted for factors influencing glycemic state (aOR).

RESULTS: Euglycemia was more common in neonates with moderate compared with severe HIE (63.6% vs 36.6%; $P < .001$). Although hypoglycemia occurred at similar rates in severe and moderate HIE (21.4% vs 19.5%; $P = .67$), hyperglycemia was more common in severe HIE (42.3% vs 16.9%; $P < .001$). Compared with euglycemic neonates, both, hypo- and hyperglycemic neonates had an increased aOR (95% confidence interval) for death or NDI (2.62; 1.47–4.67 and 1.77; 1.03–3.03) compared to those with euglycemia. Hypoglycemic neonates had an increased aOR for both death (2.85; 1.09–7.43) and NDI (2.50; 1.09–7.43), whereas hyperglycemic neonates had increased aOR of 2.52 (1.10–5.77) for death, but not NDI.

CONCLUSIONS: Glycemic profile differs between neonates with moderate and severe HIE, and initial glycemic state is associated death or NDI at 22 to 36 months.

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***A complete list of High-dose Erythropoietin for Asphyxia and Encephalopathy study group members appears in Supplemental Appendix 1.

Dr Mietzsch conceptualized and designed the study, collected data, drafted the initial manuscript, and critically reviewed and revised the manuscript; Dr Wood conceptualized and (Continued)

WHAT'S KNOWN ON THIS SUBJECT: Conflicting information exists about the independent contributions of hypo- and hyperglycemia in the first 12 hours after birth on outcome in neonates with moderate or severe hypoxic-ischemic encephalopathy.

WHAT THIS STUDY ADDS: Glycemic profiles during the first 12 hours differ between neonates with moderate and severe hypoxic-ischemic encephalopathy. Both hypo- and hyperglycemia are associated with death or neurodevelopmental impairment at 22–36 months of age after adjusting for severity of illness.

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Hypoxic-ischemic encephalopathy (HIE) affects 1 to 4:1000 live births in high-resource settings.[1] Therapeutic hypothermia (TH) is the only therapy proven to ameliorate outcomes in infants with moderate or severe HIE.[2,3] However, even with TH, nearly 50% of affected infants still die or sustain significant neurodevelopmental impairment (NDI).[4] It is therefore important to better understand differences in disease presentation and progression to develop individualized therapies and to improve outcomes.

During the transition from fetal to neonatal life, the primary energy supply switches from glucose to alternative substances such as ketones, lactate, and fatty acids.[5] Transient hypoxia occurs as part of the normal labor process, which is compensated for by activating an anaerobic metabolism, an energy costly process that requires 19 times more glucose than oxidative metabolism.[6] This adaptation is disturbed in asphyxiated infants, in whom glucose supplies are rapidly depleted.[7,8] In addition, the liver and endocrine organs, which play a significant role in glucose homeostasis in the first few hours after birth, are highly energy-dependent and commonly compromised in newborns with HIE.[8]

Recent clinical studies of infants with HIE suggest that perturbations in glycemic state such as hypoglycemia, hyperglycemia, or a combination of both are associated with unfavorable outcomes.[6,9–12] The incidence of abnormal glycemic states after HIE varies significantly across the literature, ranging from 21% to 48% for hyperglycemia, 9% to 35% for hypoglycemia, and 13% to 15% for the presence of both hyper- and hypoglycemia.[6,7,9–14] The first 6 to 12 hours of life appear to be a particularly vulnerable period in which blood glucose disturbances are associated with later unfavorable outcome.[13] Although some studies allude that both hypoglycemic and hyperglycemic episodes are associated with adverse outcome, others suggest that hypoglycemia in particular may not be independently associated with outcome.[6,10,12–14] Prior publications, which involved small sample sizes or were conducted in an era when therapeutic hypothermia was not standard of care, are therefore conflicting. In addition, few have described the full glycemic profile, including baseline glucose levels and their subsequent trajectory, in relation to outcome.

OBJECTIVES

We aimed to characterize the glycemic profile in the first 12 hours after birth and its association with death and/or neurodevelopmental impairment (NDI) in infants enrolled in the High-dose Erythropoietin for Asphyxia and Encephalopathy (HEAL) Trial.

METHODS

Data were collected as part of the phase III, multicenter, double-blinded, randomized, placebo controlled HEAL Trial.[4] The trial included 500 infants born ≥36 weeks' gestational age and treated with TH for moderate or severe HIE who were randomized to either 5 doses of erythropoietin (1000 IU/kg/dose) or placebo. Primary outcome was defined as the composite outcome of death or NDI of any severity assessed at 22 to 36 months. The window was extended from 22 to 26 months to 22 to 36 months because of the SARS-CoV-2 pandemic. Any NDI was defined as Gross Motor Function Classification System (GMFCS) level ≥1, or cerebral palsy diagnosed on a standardized neurologic exam, or Bayley Scales of Infant Toddler Development, third edition, cognitive score <90. The combined outcome of moderate or severe NDI was defined as a GMFCS level of 1 and cerebral palsy, a GMFCS level of ≥2, quadriplegic cerebral palsy, or a Bayley Scales of Infant Toddler Development, third edition, cognitive score of <85, corresponding to 1 standard deviation below the mean. Details of the trial protocol including the CONSORT diagram have been published previously.[4,15] Blood glucose measurements were performed as part of clinical practice.

Statistical Analysis

A total of 2568 glucose values were documented for 491 study subjects who had at least 1 glucose value measured in the first 12 hours after birth. Data were visually inspected and cleaned to remove spurious measurements (eg, those that occurred because of a contaminated sample from a line with concurrent dextrose administration). Unusually high-appearing blood glucose levels (>400 mg/dL) were considered contaminated and eliminated (n = 27; 1.1%) if a corresponding normal glucose level was documented within 2 hours without documented insulin administration. The remaining 2541 values were included in this analysis. Any remaining values above 400 mg/dL were winsorized to 400 mg/dL to minimize the effect of influential outliers. A histogram of the final included values, split by severity of HIE at randomization, is shown in Fig 1A. Average glucose over time stratified by severity of HIE is depicted in Fig 1B, using the locally estimated scatterplot smoothing (LOESS) method.

In previous studies of similar populations, any hypoglycemic or hyperglycemic episodes during the first 6 to 12 hours after birth were used to characterize neonates as hypoglycemic, hyperglycemic, or both. Often the hypoglycemic episode preceded the hyperglycemic episode, raising the question of whether the hyperglycemic episode was treatment induced rather than purely associated with the initial injury.[12,14] Previous studies have also used a range of values to classify infants as hypo- (<36-50 mg/dL) and hyperglycemic (>144-150 mg/dL).[6,7,9–14,16] We performed an exploratory analysis of the association between highest and lowest glucose levels for each infant in the first 12 hours after birth and the primary outcome of death or NDI, using

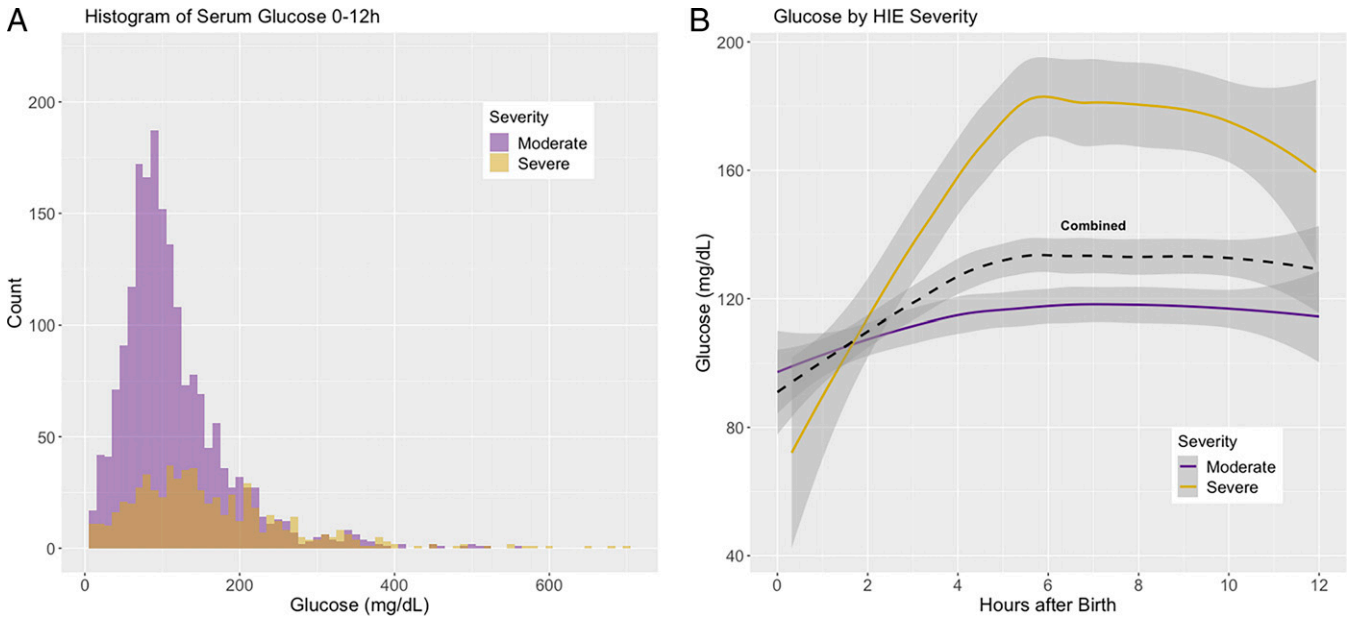

FIGURE 1

Distribution (A) and combined trajectory (B) of all blood glucose levels ($n = 2541$) obtained in the first 12 hours of life for 491 babies with moderate and severe hypoxic-ischemic encephalopathy (HIE).

LOESS curves (Fig 2A and 2B). We defined hyperglycemia as a blood glucose level of >200 mg/dL, hypoglycemia as <50 mg/dL, and euglycemia as blood glucose levels between 50 and 200 mg/dL, based on visual inspection of the LOESS curve inflection points at which >50% of neonates experienced an abnormal outcome. A similar method was used to examine average glucose profiles over time by outcome. Infants who experienced both hypo- and hyperglycemia ($n = 13$) were classified based on the abnormal glycemic state that occurred first.

To examine the association between glycemic state and outcome, we calculated the adjusted odds ratios (aOR) of death or NDI in infants who were hypo- or hyperglycemic in the first 12 hours after birth, compared with those who were euglycemic, using logistic regression. Similar analyses were performed to examine the associations between glycemic state and death and glycemic state and NDI among survivors. Sensitivity analyses were performed where infants who experienced both hypo- and hyperglycemia in the first 12 hours were removed (Supplemental Fig 5). Because blood glucose levels are influenced by severity of illness and medication exposures, models were adjusted for sentinel events during labor (shoulder dystocia, placental abruption, prolapsed cord, or uterine rupture), treatment group (erythropoietin versus placebo), small for gestational age, large for gestational age, severity of encephalopathy, 10-minute Apgar score, need for intubation, use of inotropic medications and/or hydrocortisone on day of life 1, and documented severe adverse events within 24 hours of birth, specifically disseminated intravascular coagulation (clinical bleeding warranting transfusion of blood products), intracranial hemorrhage (intraparenchymal or intraventricular blood seen on brain imaging), and severe pulmonary hypertension (requiring inhaled nitric oxide or extracorporeal membrane oxygenation). Analyses were conducted in RStudio using the R statistical package (version 4.1.2, Foundation for Statistical Computing, Vienna, Austria).[17]

RESULTS

Glucose Values and Glycemic State During the First 12 Hours After Birth

Within the first 12 hours after birth, 491 of the 500 (98.2%) trial participants had documented blood glucose values and were included in this analysis. A total of 2541 glucose values were documented in the period of interest, with a median of 5 (interquartile range, 3-6.5) values per baby. Of those, 593 (23.3%) were serum laboratory measurements, 1935 (76.2%) were point-of-care measurements and 13 (0.5%) did not have a documented measurement type. Hypoglycemia occurred in 98 (20.0%), hyperglycemia in 111 (22.6%), and euglycemia in the remaining 282 (57.4%) neonates.

Glycemic State and Glucose Profiles Stratified by Severity of Encephalopathy

Of the 491 included infants, 379 (77.2%) were diagnosed with moderate and 112 (22.8%) with severe HIE. Hyperglycemia was significantly more common among neonates with severe compared with those with moderate HIE (42.3% vs 16.9%; $P < .001$), whereas the rate of hypoglycemia was

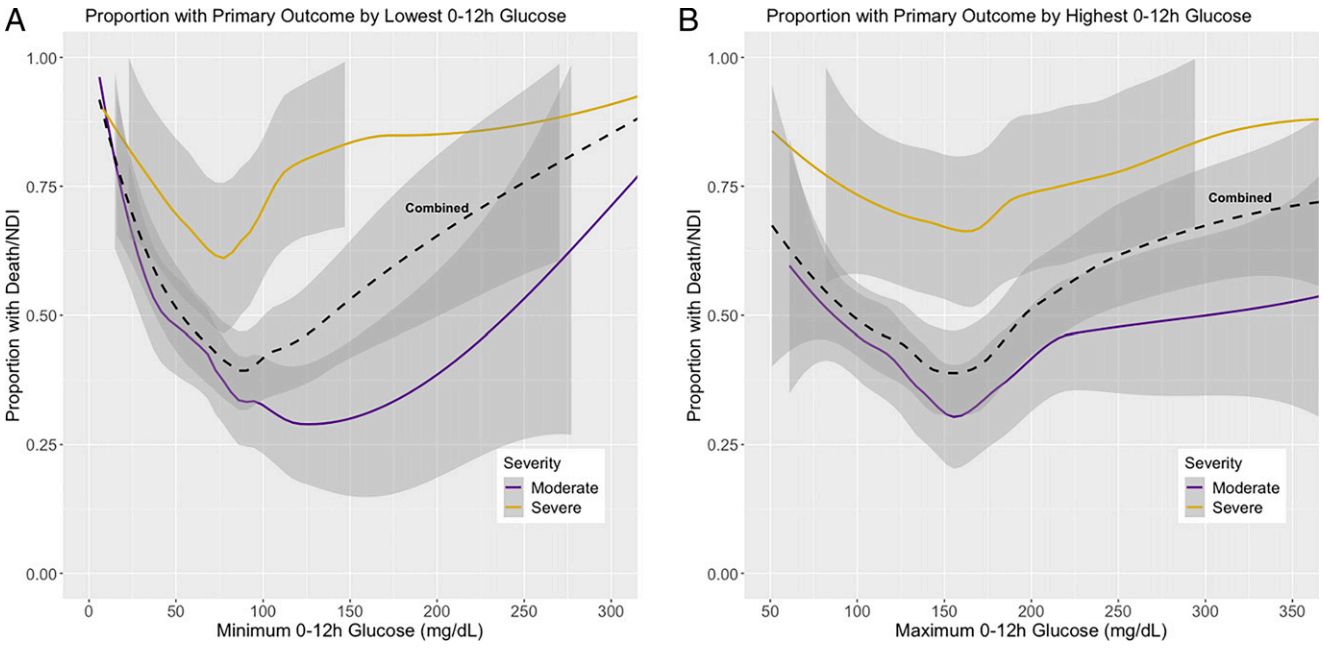

FIGURE 2

Association of primary outcome (death or NDI) with lowest (A) and highest (B) blood glucose level in the first 12 hours of life. NDI, neurodevelopmental impairment.

similar among both groups (severe, 21.4% vs moderate, 19.5%; $P = .69$).

Infants with abnormal glucose levels had a greater degree of perinatal acidosis, a higher rate of severe HIE and kidney or liver dysfunction, and a higher rate of receiving medications that may alter glucose levels such as hydrocortisone (Table 1). Compared with the percentage of euglycemic infants who experienced a documented sentinel event at birth (28%), hyperglycemic infants were more likely (35%), and hypoglycemic infants less likely (22%), to have a documented sentinel event.

Glucose profiles within the first 12 hours after birth differed between neonates with moderate and severe HIE (Fig 1A). Neonates with moderate HIE were more likely to be euglycemic compared with those with severe HIE (63.6% vs 36.6%; $P < .001$). The average blood glucose levels remained relatively constant over the first 12 hours after birth in neonates with moderate HIE, whereas mean glucose levels in neonates with severe HIE were more dynamic, with peak levels occurring by 6 hours followed by a plateau period before decreasing again around 10 to 12 hours after birth (Fig 1B). Additionally, infants with severe HIE had a much wider range of initial blood glucose measurements and, on average, a lower initial blood glucose than those with moderate HIE (Fig 1B).

Minimum and Maximum Blood Glucose Levels in Relation to Outcome

Outcome data at 22 to 36 months was available for 472/491 (96.1%). Both minimum and maximum measured blood glucose levels during the first 12 hours after birth were associated with death or NDI, with U-shaped associations between highest/lowest glucose and death/NDI (Fig 2A and 2B). Qualitatively, infants with blood glucose levels <25 mg/dL had the highest rates of abnormal long-term outcome. An increased proportion of death or NDI was also seen in infants with a minimum glucose value >200 mg/dL (Fig 2A). Maximum blood glucose levels in the first 12 hours after birth were also associated with death or moderate-severe NDI (Fig 2B). Infants with a maximum blood glucose level >200 mg/dL had increasing adverse primary outcome proportional to the maximum blood glucose level.

Glucose Trajectory and Primary Outcome

When separated by outcome, average glucose profiles in the first 12 hours of life showed notable differences (Fig 3). Neonates who died displayed group-averaged initial blood glucose levels of approximately 65 mg/dL, which increased to nearly 200 mg/dL on average by 6 hours after birth and remained higher than the other outcome groups for the majority of the 12-hour period. In contrast, neonates who survived without NDI had average initial glucose levels of approximately 100 mg/dL, which increased to approximately 125 to 130 mg/dL on average at 4 to 6 hours before slowly declining again. Those who survived with any NDI displayed group-averaged glucose levels between the other 2 outcome categories; initial average blood glucose was around

TABLE 1 Demographics and Patient Characteristics

	Overall	Euglycemia	Hypoglycemia (<50 mg/dL)	Hyperglycemia (>200 mg/dL)
	N = 491	*N* = 282	*N* = 98	*N* = 111
Maternal age, mean (SD)	29.6 (6.3)	29.5 (6.5)	29.6 (6.2)	29.9 (6.0)
Maternal education				
High school or less	182 (37.1)	101 (35.8)	44 (44.9)	37 (33.3)
Some college	105 (21.4)	58 (20.6)	23 (23.5)	24 (21.6)
College graduate or higher	173 (35.2)	113 (40.1)	24 (24.5)	36 (32.4)
Not reported	31 (6.3)	10 (3.5)	7 (7.1)	14 (12.6)
Maternal parity				
1	282 (57.4)	171 (60.6)	45 (45.9)	52 (46.8)
2	106 (21.6)	59 (20.9)	24 (24.5)	29 (26.1)
3+	103 (21.0)	52 (18.4)	29 (29.6)	22 (19.8)
Pregnancy complications				
Pregnancy-induced hypertension	57 (11.6)	29 (10.3)	15 (15.3)	13 (11.7)
Preeclampsia	44 (9.0)	29 (10.3)	12 (12.2)	3 (2.7)
Gestational diabetes/insulin-dependent diabetes mellitus	55 (11.2)	36 (12.8)	12 (12.2)	7 (6.3)
Thyroid disease	39 (7.9)	22 (7.8)	8 (8.2)	9 (8.1)
Gestational age, mean (SD)	39.1 (1.4)	39.2 (1.4)	38.6 (1.5)	39.5 (1.4)
Birth weight (kg), mean (SD)	3.4 (0.6)	3.4 (0.6)	3.4 (0.7)	3.4 (0.5)
Small for gestational age	61 (12.4)	35 (12.4)	17 (17.3)	9 (8.1)
Large for gestational age	74 (15.1)	39 (13.8)	23 (23.5)	12 (10.8)
Male sex	269 (54.8)	154 (54.6)	57 (58.2)	58 (52.3)
Labor and delivery complications				
Chorioamnionitis	64 (13.0)	41 (14.5)	9 (9.2)	14 (12.6)
Sentinel event	140 (28.5)	79 (28.0)	22 (22.4)	39 (35.1)
Placenta abruption	70 (14.3)	35 (12.4)	13 (13.3)	12 (10.8)
Cord prolapse	21 (4.3)	15 (5.3)	1 (1.0)	5 (4.5)
Uterine rupture	24 (4.9)	12 (4.3)	2 (2.0)	10 (9.0)
Shoulder dystocia	32 (6.5)	20 (7.1)	6 (6.1)	6 (5.4)
Delivery mode				
Vaginal delivery				
Spontaneous	117 (23.8)	77 (27.3)	14 (14.3)	26 (23.4)
Instrumented	51 (10.4)	33 (11.7)	5 (5.1)	13 (11.7)
Cesarean delivery				
Elective	12 (2.4)	9 (3.2)	2 (2.0)	1 (0.9)
Emergent or urgent	311 (63.3)	163 (57.8)	77 (78.6)	71 (64.0)
Apgar (median, IQR)				
5 min	3 (2–5)	4 (2–5)	3 (2–5)	3 (1–4)
10 min	5 (3–7)	5 (4–7)	5 (3–7)	4 (2–5)
Worst blood gas parameters[a]				
pH, mean (SD)	6.93 (0.17)	6.95 (0.16)	6.92 (0.17)	6.88 (0.20)
Base deficit, mean (SD)	−18.4 (6.2)	−17.3 (5.8)	−19.3 (6.0)	−20.4 (6.9)
Resuscitation measures				
Intubation	341 (69.5)	183 (64.9)	68 (69.4)	90 (81.1)
Cardiac compressions	156 (31.8)	71 (25.2)	29 (29.6)	56 (50.5)
Epinephrine	207 (42.2)	115 (40.8)	52 (53.1)	40 (36.0)
Placenta pathology				
Chorioamnionitis	123 (25.1)	73 (25.9)	19 (19.4)	31 (27.9)
Any abnormality	269 (54.8)	145 (51.4)	62 (63.3)	62 (55.9)
Any acute abnormality	202 (41.1)	117 (41.5)	40 (40.8)	45 (40.5)
Worst Sarnat stage within 6 h of birth				
Moderate	379 (77.2)	241 (85.5)	74 (75.5)	64 (57.7)
Severe	112 (22.8)	41 (14.5)	24 (24.5)	47 (42.3)

TABLE 1 Continued

	Overall	Euglycemia	Hypoglycemia (<50 mg/dL)	Hyperglycemia (>200 mg/dL)
	N = 491	*N* = 282	*N* = 98	*N* = 111
Blood glucose (mg/dL)				
First glucose	126 (68)	106 (59)	96 (59)	152 (82)
0-6 h (lowest)	100 (67)	99 (33)	34 (28)	167 (85)
0-6 h (highest)	149 (73)	127 (37)	102 (54)	244 (67)
6-12 h (lowest)	86 (54)	86 (26)	29 (13)	138 (75)
6-12 h (highest)	163 (75)	132 (36)	129 (58)	271 (62)
End-organ injury (during hospitalization)				
Liver injury (AST >100 IU/L)	197 (40.1)	90 (31.9)	60 (61.2)	47 (42.3)
Disseminated intravascular coagulopathy (INR >2.0)	156 (31.8)	61 (21.6)	48 (49.0)	47 (42.3)
Acute kidney injury (creatinine >1.5× baseline)	56 (11.4)	24 (8.5)	17 (17.3)	15 (13.5)
Thrombocytopenia (platelet count <100 K $\times 10^9$/L)	201 (40.9)	91 (32.3)	65 (66.3)	45 (40.5)
Extracorporeal membrane oxygenation	19 (3.9)	7 (2.5)	2 (2.0)	10 (9.0)
Persistent pulmonary hypertension	86 (17.5)	38 (13.5)	24 (24.5)	24 (21.6)
Medications (first day after birth)				
Inotropic support	165 (33.6)	69 (24.5)	46 (46.9)	47 (42.3)
Hydrocortisone	69 (14.1)	4 (0.1)	4 (4.1)	17 (15.3)
Insulin	25 (5.1)	4 (1.4)	4 (4.1)	17 (15.3)
Seizures	181 (36.9)	81 (28.7)	49 (50.0)	51 (45.9)
Erythropoietin treatment	251 (51.1)	140 (49.6)	55 (56.1)	56 (50.5)
Laboratory values (first day)				
Hematocrit (%) (lowest)	42.0 (9.1)	42.8 (8.6)	42.3 (10.5)	39.8 (8.7)
Platelet count ($\times 10^9$/L) (lowest)	159 (68)	176 (60)	121 (64)	150 (73)
White blood cell count ($\times 10^9$/L) (highest)	17.8 (8.4)	18.0 (7.9)	16.5 (8.8)	18.5 (9.3)
Outcomes				
Combined primary outcome	239 (48.7)	108 (38.3)	61 (62.2)	70 (63.1)
Death or NDI				
Death	64 (13.0)	18 (6.4)	17 (17.3)	29 (26.1)
Any NDI	175 (35.6)	90 (31.9)	44 (44.9)	41 (36.9)
Moderate or severe NDI	119 (24.1)	58 (20.6)	33 (33.7)	28 (25.2)
Lost to follow-up	19 (3.9)	14 (5.0)	4 (4.1)	1 (0.9)

Abbreviations: AST, aspartate transaminase; IQR, interquartile range; NDI, neurodevelopmental impairment; SD, standard deviation.
[a]Measured on arterial or venous umbilical cord blood or a neonatal sample obtained within 1 h after birth.

85 mg/dL, increasing over the 12-hour period to approximately 135 mg/dL.

Glycemic State and Primary Outcome

Euglycemic neonates were least likely to experience an adverse outcome of death or NDI and were used as the reference group. Primary outcome was more likely to occur in neonates with hypoglycemia (aOR, 2.62; 95% confidence interval [CI], 1.5–4.67) and hyperglycemia (aOR, 1.77; 95% CI, 1.03–3.03) (Fig 4). When separating primary outcome by death and NDI, neonates with hypoglycemia had an increased risk of both death (aOR, 2.85; 95% CI, 1.09–7.43) and NDI in survivors (aOR, 2.50; 95% CI, 1.09–7.43). In contrast, neonates with hyperglycemia had a significantly increased risk of death (aOR, 2.52; 95% CI, 1.10–5.77), but not NDI (Fig 4B and C). Removing infants who experienced both hypo- and hyperglycemia, did not alter the results (sensitivity analyses; Supplemental Fig 5).

DISCUSSION

In this large cohort, we show that glucose profiles in the first 12 hours after birth differ in neonates with moderate versus severe encephalopathy and that baseline values are associated with severity of illness. After adjusting for severity of illness and degree of encephalopathy, early glycemic state was still associated with primary outcome at 22 to 36 months. Specifically, hypoglycemia was associated with both mortality and higher rates of NDI in survivors, whereas hyperglycemia during the 12 hours following birth was associated with an increased risk of death, but not NDI.

Hypoglycemic and hyperglycemic states have both been reported to be associated with adverse outcome in newborns affected by moderate to severe HIE.[6,12,13] Although many studies have assessed hypoglycemia and hyperglycemia as contributing or causative factors for adverse outcome, few studies have investigated glycemic trends and profiles during the first 12 hours after birth. Emerging

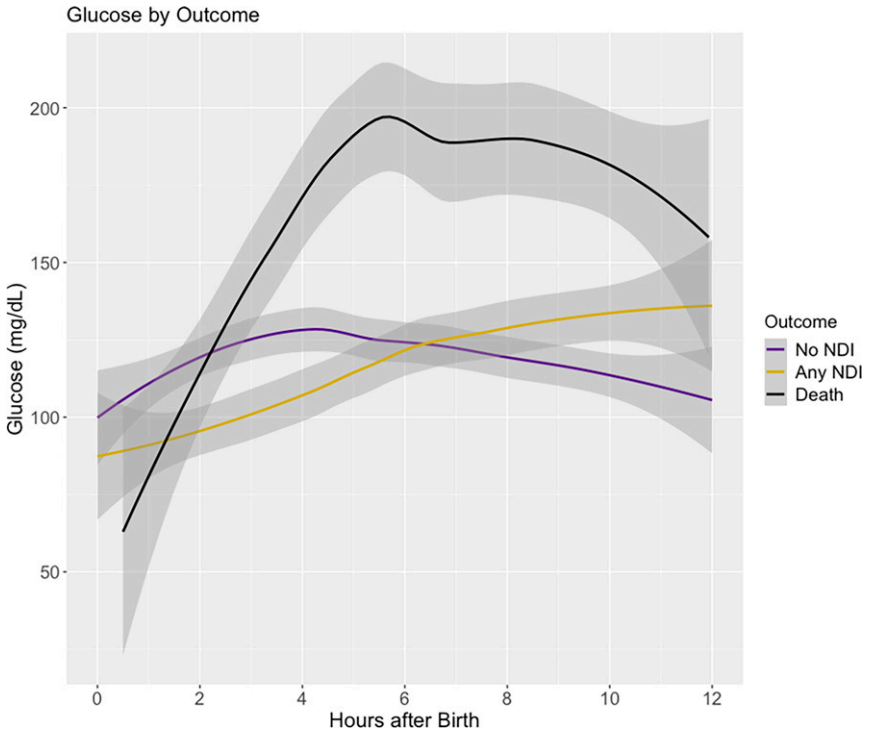

FIGURE 3

Combined glucose profile during the first 12 hours after birth displayed by outcome category: survival without NDI (purple) vs any NDI (gold) or death (black). NDI, neurodevelopmental impairment.

literature on small patient samples supports the idea that timing and duration of injury might determine which neonates become hypoglycemic versus hyperglycemic.[9,12] Our data suggest that healthier babies display a greater ability to compensate for the increasing metabolic demands of HIE and can achieve glucose homeostasis despite a perinatal insult. In comparison, sicker babies with HIE maintain a higher baseline blood glucose concentration, have greater glucose lability in the first 12 hours after birth, and these findings are associated with unfavorable outcomes. These results are similar to those described in a post hoc analysis of the CoolCap trial and in a small prospective study by Montaldo et al, both of which showed that newborns who have glucose lability in the first 12 hours have a trend toward unfavorable outcome.[6,12]

Early hypoglycemia within the first 6 to 12 hours of life has been shown in several studies to be associated with severity of HIE and gravity of metabolic acidosis, suggesting that early hypoglycemia may reflect depleted fetal glucose stores and/or inadequate gluconeogenesis secondary to multiorgan dysfunction.[9,14,16,18] This theory is supported by previous observations that markers of liver

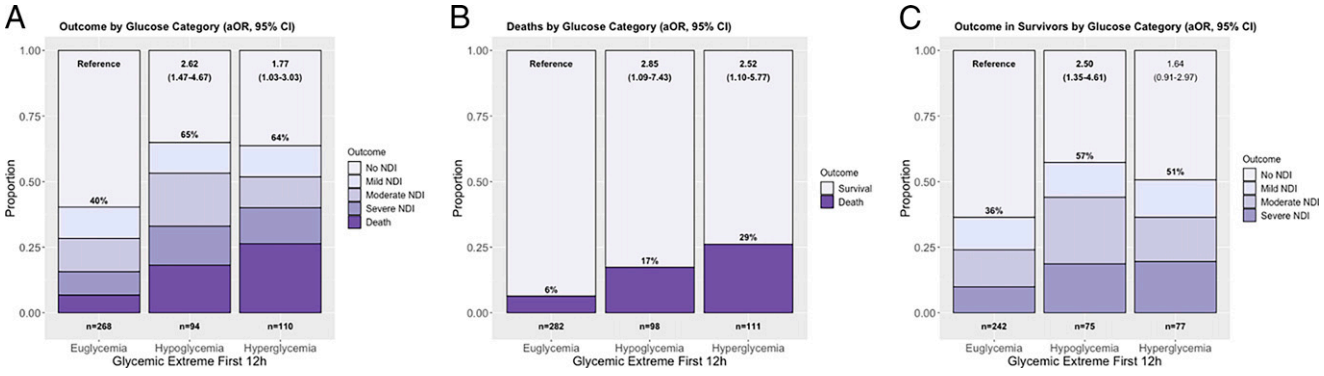

FIGURE 4

Outcome by glucose status within the first 12 hours of life, using euglycemic state as reference. (A) Combined primary outcome of death and any NDI for each glycemic state. (B) Survival versus nonsurvival by glycemic state. (C) Outcome in survivors by glycemic state. 95% CI, 95% confidence interval; aOR, adjusted odds ratio; NDI, neurodevelopmental impairment.

injury are more prominent in hypoglycemic neonates, which was also the case in our cohort.[16] A decreased ability to mobilize glycogen stores or undergo gluconeogenesis may result in decreased ability to compensate during transition from fetal to neonatal life, exacerbating any accompanying hypoxic-ischemic injury. Furthermore, hypoglycemia is associated with an injury pattern on magnetic resonance imaging that is consistent with prolonged and partial ischemic insults, a higher rate of neurodevelopmental impairment in survivors, as well as concern for less effectiveness of TH in this population, which may further hint at a subacute and prolonged injury underlying the acute presentation.[7,9,13,14,16] Hypoglycemia in neonates with moderate or severe HIE often presents in conjunction with other markers of end-organ injury, indicating a multiorgan insult that therefore might suggest that hypoglycemia can be seen as a marker of severity of injury. For example, several studies found that hypoglycemia was no longer significantly associated with adverse outcome in HIE after adjusting for severity of illness.[13,19] However, previous studies had significantly smaller sample sizes and were conducted partially before the era of TH. In the current study, we adjusted for markers of severity of illness including degree of encephalopathy and organ dysfunction, and the results indicate that hypoglycemia appears to be independently associated with an increased adverse long-term outcome compared with euglycemic newborns, but to a lesser degree than those who experience hyperglycemia.

The relationship between hyperglycemia and outcomes in neonates with HIE has not been widely studied yet, possibly because the commonly used definition of hyperglycemia may have resulted in inclusion of a significant proportion of glucose levels in the 150- to 200-mg/dL range, for which pharmacological interventions such as insulin are rarely indicated. We defined hyperglycemia as >200 mg/dL according to clinical significance determined by visual inspection of continuous LOESS curves of average highest glucose and proportion of infants experiencing death/NDI. Using this clinically meaningful cutoff, we show that hyperglycemia is not only associated with a significantly higher rate of death but also that more severely affected newborns have higher median blood glucose levels than their less-compromised peers.

Hyperglycemia in the early stages of asphyxia may reflect depressed cerebral glucose uptake and acute ongoing utilization of adenosine triphosphate and H^+ release as suggested by lower measured pH values.[9,20] The hypothesis that hyperglycemia may reflect a very acute and recent insult is supported by a study in piglets where glucose levels increased threefold immediately following asphyxia.[19] These findings are similar to those seen after cardiac arrest or traumatic brain injury in animals, adults, and pediatric patients in which hyperglycemia has been associated with a more profound brain injury.[21–25] Early hyperglycemia has also been more commonly reported in cases of HIE with an identified acute sentinel event, which appeared to be the case in our cohort, in which 35% of hyperglycemic infants had a documented sentinel event compared with 28% of euglycemic and 22% of hypoglycemic infants.[9] Additionally, the post hoc analysis of the CoolCap trial demonstrated that TH was more effective in hyperglycemic infants, supporting the theory that hyperglycemia is associated with more recent acute asphyxial events.[9]

This study has several limitations. The lack of a standard approach to glucose sampling could have caused sampling bias driven by extreme values resulting in more frequent sampling. The HEAL dataset did not include daily markers of liver and kidney function, and although we adjusted for a number of factors reflecting severity of illness, residual confounding may still be present. Additionally, the observational nature of this study precludes any conclusions regarding whether correction of either hypo- or hyperglycemia would improve outcomes. A significant strength of this study is that the HEAL Trial dataset is the largest cohort with standardized follow-up available to elucidate the potential causation and impact of deranged glycemic states in neonates with moderate or severe HIE undergoing TH. In contrast to many of the published studies, we had the opportunity to established cutoffs of hypo- and hyperglycemia that appeared to be more directly associated with outcomes and to adjust for severity of illness to eliminate its potential confounding effect on the glycemic state. As a result, we were able to show that both hyper- and hypoglycemia are independently associated with adverse long-term outcomes.

CONCLUSIONS

Glycemic profiles during the first 12 hours after birth differ between neonates with moderate and severe HIE. Both hypo- and hyperglycemia were associated with an increased risk of death after adjusting for severity of illness. Among survivors, hypoglycemia was also independently associated with an increased risk of NDI at 22 to 36 months of age.

ABBREVIATIONS

aOR: adjusted odds ratio
BG: blood glucose
CI: confidence interval
GMFCS: Gross Motor Function Classification System
HEAL: High-dose Erythropoietin for Asphyxia and Encephalopathy
HIE: hypoxic-ischemic encephalopathy
LOESS: locally estimated scatterplot smoothing
NDI: neurodevelopmental impairment
TH: therapeutic hypothermia

designed the study, carried out the statistical analyses, drafted the initial manuscript, and critically reviewed and revised the manuscript; Dr Wu conceptualized and designed the study, collected data, and critically reviewed and revised the manuscript; Dr Natarajan collected data and critically reviewed and revised the manuscript; Dr Glass critically reviewed and revised the manuscript; Dr Gonzalez collected data and critically reviewed and revised the manuscript; Dr Mayock collected data and critically reviewed and revised the manuscript; Mr Comstock coordinated and supervised data collection, carried out the initial analyses, critically reviewed and revised the manuscript; Dr Heagerty coordinated and supervised data collection, carried out the initial analyses and critically reviewed and revised the manuscript; Dr Juul conceptualized and designed the study, collected data, and critically reviewed and revised the manuscript; Dr Wu conceptualized and designed the study, collected data, and critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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REFERENCES

1. Kurinczuk JJ, White-Koning M, Badawi N. Epidemiology of neonatal encephalopathy and hypoxic-ischaemic encephalopathy. *Early Hum Dev.* 2010;86(6):329–338
2. 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
3. Azzopardi DV, Strohm B, Edwards AD, et al; TOBY Study Group. Moderate hypothermia to treat perinatal asphyxial encephalopathy. *N Engl J Med.* 2009;361(14):1349–1358
4. Wu YW, Comstock BA, Gonzalez FF, et al; HEAL Consortium. Trial of erythropoietin for hypoxic-ischemic encephalopathy in newborns. *N Engl J Med.* 2022;387(2):148–159
5. Adamkin DH; Committee on Fetus and Newborn. Postnatal glucose homeostasis in late-preterm and term infants. *Pediatrics.* 2011;127(3):575–579
6. Basu SK, Kaiser JR, Guffey D, Minard CG, Guillet R, Gunn AJ; CoolCap Study Group. Hypoglycaemia and hyperglycaemia are associated with unfavourable outcome in infants with hypoxic ischaemic encephalopathy: a post hoc analysis of the CoolCap Study. *Arch Dis Child Fetal Neonatal Ed.* 2016;101(2):F149–F155
7. Salhab WA, Wyckoff MH, Laptook AR, Perlman JM. Initial hypoglycemia and neonatal brain injury in term infants with severe fetal acidemia. *Pediatrics.* 2004;114(2):361–366
8. Boardman JP, Hawdon JM. Hypoglycaemia and hypoxic-ischaemic encephalopathy. *Dev Med Child Neurol.* 2015;57(suppl 3):29–33
9. Basu SK, Salemi JL, Gunn AJ, Kaiser JR; CoolCap Study Group. Hyperglycaemia in infants with hypoxic-ischaemic encephalopathy is associated with improved outcomes after therapeutic hypothermia: a post hoc analysis of the CoolCap Study. *Arch Dis Child Fetal Neonatal Ed.* 2017;102(4):F299–F306
10. Tan JKG, Minutillo C, McMichael J, Rao S. Impact of hypoglycaemia on neurodevelopmental outcomes in hypoxic ischaemic encephalopathy: a retrospective cohort study. *BMJ Paediatr Open.* 2017;1(1):e000175
11. Tam EW, Haeusslein LA, Bonifacio SL, et al. Hypoglycemia is associated with increased risk for brain injury and adverse neurodevelopmental outcome in neonates at risk for encephalopathy. *J Pediatr.* 2012;161(1):88–93
12. Montaldo P, Caredda E, Pugliese U, et al. Continuous glucose monitoring profile during therapeutic hypothermia in encephalopathic infants with unfavorable outcome. *Pediatr Res.* 2020;88(2):218–224
13. Nadeem M, Murray DM, Boylan GB, Dempsey EM, Ryan CA. Early blood glucose profile and neurodevelopmental outcome at two years in neonatal hypoxic-ischaemic encephalopathy. *BMC Pediatr.* 2011;11:10
14. Parmentier CEJ, de Vries LS, van der Aa NE, et al. Hypoglycemia in infants with hypoxic-ischemic encephalopathy is associated with additional brain injury and worse neurodevelopmental outcome. *J Pediatr.* 2022;245:30–38.e1
15. Juul SE, Comstock BA, Heagerty PJ, et al. High-Dose Erythropoietin for Asphyxia and Encephalopathy (HEAL): a randomized controlled trial - background, aims, and study protocol. *Neonatology.* 2018;113(4):331–338

16. Basu SK, Ottolini K, Govindan V, et al. Early glycemic profile is associated with brain injury patterns on magnetic resonance imaging in hypoxic ischemic encephalopathy. *J Pediatr.* 2018;203:137–143

17. R Development Core Team. A language and environment for statistical computing. Available at: www.R-project.org/. Accessed May 12, 2023

18. Basu P, Som S, Choudhuri N, Das H. Contribution of the blood glucose level in perinatal asphyxia. *Eur J Pediatr.* 2009;168(7):833–838

19. Randall GC. Studies on the effect of acute asphyxia on the fetal pig in utero. *Biol Neonate.* 1979;36(1-2):63–69

20. Hochachka PW, Mommsen TP. Protons and anaerobiosis. *Science.* 1983;219(4591):1391–1397

21. Chopp M, Welch KM, Tidwell CD, Helpern JA. Global cerebral ischemia and intracellular pH during hyperglycemia and hypoglycemia in cats. *Stroke.* 1988;19(11):1383–1387

22. Myers RE, Yamaguchi S. Nervous system effects of cardiac arrest in monkeys. Preservation of vision. *Arch Neurol.* 1977;34(2):65–74

23. Daviaud F, Dumas F, Demars N, et al. Blood glucose level and outcome after cardiac arrest: insights from a large registry in the hypothermia era. *Intensive Care Med.* 2014;40(6):855–862

24. Moler FW, Donaldson AE, Meert K, et al; Pediatric Emergency Care Applied Research Network. Multicenter cohort study of out-of-hospital pediatric cardiac arrest. *Crit Care Med.* 2011;39(1):141–149

25. Elkon B, Cambrin JR, Hirshberg E, Bratton SL. Hyperglycemia: an independent risk factor for poor outcome in children with traumatic brain injury. *Pediatr Crit Care Med.* 2014;15(7):623–631