Hyperglycaemia and outcome in neonates with hypoxic-ischaemic encephalopathy

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Background. Hypoxic-ischaemic encephalopathy (HIE) remains a leading cause of death and disability in term neonates despite therapeutic hypothermia. Hyperglycaemia in the first 12 hours of life is associated with poor outcomes in some studies. This relationship has not yet been explored in South African (SA) cohorts.
Objective. To describe the association between hyperglycaemia (in the first 12 hours of life) and poor outcome, which was defined as death or a severely abnormal amplitude-integrated electroencephalogram (aEEG) at 48 hours, in neonates with moderate-to-severe HIE who were treated with hypothermia at an SA tertiary hospital.
Methods. Folders from a database of 57 neonates with moderate-to-severe HIE treated with hypothermia between January 2011 and December 2012, were reviewed to obtain glycaemic profiles. Maternal and neonatal characteristics and outcomes were extracted from the database.
Results. Only 47 neonates had adequate glucose and aEEG data. Seventeen neonates (36%) had hyperglycaemia (>8.3 mmol/L), 25 (53%) were normoglycaemic and 5 neonates (10%) were hypoglycaemic (<2.3 mmol/L). Hyperglycaemia was only associated with death or severely abnormal aEEG at a glucose value ≥25.6 mmol/L. Hyperglycaemia was significantly associated with a low 5-minute Apgar score (p=0.007), severely abnormal aEEG at 6 hours (p=0.029), and a higher HIE score at 6 hours (p=0.002). Hyperglycaemia was associated with death (odds ratio 10; 95% confidence interval 1 - 96; p=0.045), but the association was not independent of the 5-minute Apgar score.
Conclusion. Early hyperglycaemia in neonates with moderate-to-severe HIE was associated with disease severity at birth and death despite cooling.

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Hypoxic-ischaemic encephalopathy (HIE) is a leading cause of death and neurodevelopmental disability in term neonates.[1-4] Despite the association of therapeutic hypothermia (TH) with a significant reduction in mortality, many neonates with moderate-to-severe HIE survive with disability.[1,2] This suggests there may be additional factors causing neuronal damage, which may contribute to the severity of HIE and/or the response to TH.

Glucose is the primary energy substrate for brain metabolism in the newborn with encephalopathy. Neonatal hypoglycaemia is an independent risk factor for adverse outcome in both preterm and term neonates – potentially mediated via oxidative stress causing neuronal damage of both white and grey matter.[5-7] Hyperglycaemia following asphyxia is thought to occur as a result of prolonged elevation of stress hormones associated with secondary reperfusion injuries in an energy-depleted cell leading to neuronal apoptosis.[8] Hyperglycaemia may therefore serve as a proxy for severity of brain injury in neonates with HIE.[9]

Two small retrospective studies reported differing conclusions on the association between early hyperglycaemia and unfavorable outcomes in neonates with HIE. Nadeem *et al.*[8] found that hyperglycaemia in the first 6 hours of life was not associated with unfavorable outcome.Spies *et al.*[10] found that hyperglycaemia in the first 12 hours of life was associated with poor gross motor deficits.
In a post hoc analysis of the Cool Cap Study and glycaemic control, Basu *et al.*[9] found that the odds of death or severe disability were increased in neonates with either hypoglycaemia defined as blood glucose <2.3 mmol/L (odds ratio (OR) 6.2; 95% confidence interval (CI) 1.4 - 27.3) or hyperglycaemia defined as >8.3 mmol/L (OR 2.7; 95% CI 1.5 - 4.9) during 12 hours after randomisation, compared with normoglycaemic neonates. These associations were independent of encephalopathy grade, obstetric and delivery history and the use of TH. A further analysis of the same study showed that hyperglycaemic neonates had the highest incidence of sentinel events, and they were the only group to significantly benefit from TH.[11]

The aim of the present study was to explore the association between hyperglycaemia and outcomes in a cohort of neonates with moderate-severe HIE who were treated with TH in a tertiary hospital in South Africa (SA). The primary objective of the present study was to describe the association between hyperglycaemia during the first 12 hours of life and poor outcome. Secondary objectives were to: describe the demographic, obstetric and neonatal characteristics; describe the frequency of hyperglycaemia and hypoglycaemia during the first 12 hours of life; determine if hyperglycaemia was associated with obstetric or neonatal variables; and to determine if hyperglycaemia was associated with the individual secondary poor outcome measures of either death or severely abnormal amplitude-integrated electroencephalogram (aEEG) at 48 hours.

Methods

Study design and ethical approval

The study is a retrospective observational folder review and data analysis of a pre-existing cohort and database of neonates with moderate to severe HIE, who were treated with TH and formed the basis of a previous study on the influence of birth site on outcome.[12] The University of Cape Town (UCT) Health Sciences Faculty Human Research Ethics Committee approved the databases for the pre-existing cohort (ref. no. HREC 612/2013) and this study, with access to the previous database (ref. no. HREC 245/2020). Informed consent was not required as the study was a retrospective analysis of de-identified data.

Study population

The cohort included all neonates, both inborn and outborn, with moderate-to-severe HIE admitted to Groote Schuur Hospital (GSH) Neonatal Intensive Care Unit (NICU) in Cape Town, SA, over a two-year period from January 2011 to December 2012, all of whom were treated with TH. The GSH neonatal unit has ~2 000 admissions per annum and is the major tertiary referral centre for the Metro West Area of Cape Town.

Management was standardised according to a written protocol. All neonates were initially commenced on an intravenous premixed 10% dextrose and potassium-free electrolyte solution and were fluid-restricted to a total fluid intake (TFI) of 40 mL/kg. Vital signs were monitored continuously; blood glucose was checked on admission and monitored 4-hourly thereafter. If hypoglycaemia occurred, the concentration of dextrose in intravenous fluid was increased while maintaining a TFI of 40 mL/kg. Neonates were cooled using either a Tecotherm Neo (TEC COM GmbH, Germany) in servo-control mode (constant rectal temperature monitoring) cooling mat or a servo-controlled gel-bag cooling system,[13] depending on availability.

All neonates were monitored with two-channel aEEG within the first 6 hours of life. Monitoring was continued for at least the 72-hour duration of TH. The aEEG data were already reviewed and interpreted in the earlier study.[12] Five different background aEEG patterns are recognised: continuous normal voltage (CNV); discontinuous normal voltage (DNV); burst suppression (BS); low voltage (LV) and flat trace (FT).[14] In the present study, we refer to the DNV, BS, LV and FT patterns collectively as an abnormal aEEG and we defined a subgroup with severely abnormal EEG if the background was BS, LV or FT at age 6 hours. A severely abnormal aEEG defined in this way, that persists to age 48 hours in neonates who are treated with TH, has a 100% positive predictive value for death or severe disability.[15]

The severity of encephalopathy was assessed before TH by age 6 hours of life and daily until day seven or discharge, whichever occurred earliest. The encephalopathy was assessed using the Thompson HIE score[16] and the modified Sarnat grading system.[13,17] The Thompson Score is based on nine aspects of the neurological examination of neonates with HIE – it ranges from 0 to 22. The modified Sarnat grading system defines encephalopathy as the presence of one or more signs in at least three of the following six categories: level of consciousness; spontaneous activity; posture; tone; primitive reflexes; and autonomic nervous system. The number of mild, moderate or severe signs determines the final grade; however, if the signs are equally distributed, the grade is based on the level of consciousness.[13,17]

Inclusion criteria

All the following criteria (A, B and C) were required for provision of TH and for study inclusion in both the pre-existing dataset and the current study.

A. Gestation ≥36 weeks, birthweight ≥1 800 g and able to start cooling at age ≤6 hours.
B. Suspected/potential intrapartum hypoxia, suggested by at least one of the following:
   - 5-minute Apgar score<7 and/or
   - ongoing respiratory support at 10 minutes and/or
   - cord or neonatal blood gas assessment within 60 minutes of birth with pH≤7 or base deficit of ≥12 mmol/L.
C. Signs of moderate-to-severe encephalopathy during the first 6 hours of life indicated by at least one of the following:
   - three signs of moderate-severe HIE defined by Shankaran[17] and/or
   - depressed level of consciousness plus abnormal tone and/or
   - clinical seizures and/or
   - abnormal aEEG defined by at least one of: DNV, BS, LV, FT or seizures.

Exclusion criteria

Neonates with any of the following conditions were excluded: severe congenital/chromosomal anomaly; congenital infection; persistent pulmonary hypertension of the newborn not responding to treatment; systemic hypotension or bleeding not responding to treatment; and moribund neonates who were therefore unlikely to benefit from cooling. In addition, if there were insufficient aEEG or glucose data (a minimum of two blood glucose levels documented at any time during the first 12 hours of life) available within the cohort of 57 neonates, these neonates were excluded from the present study.

Sample size and data collection

Convenience sampling was used, as the study was descriptive and limited to the pre-existing database which contained 57 records.[12] Demographic, obstetric and neonatal data were collected from a pre-existing database and hospital folders were reviewed to obtain blood glucose measurements within the first 12 hours of life from nursing charts, paramedic transfer scripts, delivery notes and neonatal admission notes. The following data were also collected from the database: pregnancy and intrapartum complications, sex, birthweight, resuscitation data, aEEG and clinical encephalopathy assessment data prior to therapeutic hypothermia, before or at 6 hours, age at initiation of cooling, the occurrence of hypotension, pulmonary hypertension, need for mechanical ventilation, late-onset sepsis, necrotising enterocolitis, aEEG data at 48 hours, presence of seizures and mortality. The variables were limited by the extent of the existing database. Data were de-identified and transcribed into a password-controlled Excel (Microsoft Corp., USA) spreadsheet and patient folder numbers were matched to study numbers on a separate spreadsheet.

Definitions

Poor outcome was defined as death or severely abnormal aEEG at 48 hours. For the purpose of the present study, hyperglycaemia was defined as a blood glucose level >8.3 mmol/L and hypoglycaemia was defined as a blood glucose level <2.3 mmol/L – these parameters were chosen to facilitate comparison with previous publications.[9] A sentinel event was defined as any of the following: placental abruption; head entrapment; prolapse cord; ruptured uterus; shoulder dystocia or maternal hypoxia/hypotension. An abnormal fetal heart rate was defined as a non-reassuring or abnormal cardiotocograph (CTG) or fetal bradycardia (<100 bpm) or delayed decelerations on auscultation.

Data Analysis

Stata version 12 (Stata Corp., USA) was used for statistical analyses. The chi square or Fischer's exact tests were used to compare categorical variables and Student's *t*-test and the Wilcoxon rank-sum test were used for comparison of parametric and non-parametric continuous variables, respectively. The association of at least one occurrence of hyperglycaemia during the first 12 hours of life with outcomes was determined. The association between hyperglycaemia and death was further assessed using logistic regression in a model that included neonatal characteristics at birth that were associated with hyperglycaemia with a *p*-value <0.1. Receiver operating curve (ROC) analysis was performed to determine the relationship between the highest blood sugar in the first 12 hours and the combined outcome of death or severely abnormal aEEG at 48 hours. All tests were two-sided and statistical significance was assigned at $p<0.05$.

Results

There were 57 neonates with moderate-severe HIE in the original database but only 47 met inclusion criteria; 10 neonates were excluded owing to insufficient glucose or aEEG data.

Maternal and neonatal characteristics

The baseline maternal and neonatal characteristics are shown in Table 1. Thirty-two neonates (68%) were outborn. Seventeen neonates (36%) had at least one episode of hyperglycaemia in the first 12 hours of life and none of these neonates had hypoglycaemia. Twenty-five neonates (53%) were normoglycaemic. Only five neonates had hypoglycaemia in the first 12 hours – 80% were inborn. None of the hypoglycaemic neonates had an abnormal short-term outcome and they were excluded from comparative analyses between normoglycaemic and hyperglycaemic neonates, therefore a comparative cohort of 42 neonates remained.

Eleven of the 42 (26%) with normo- or hyperglycaemia were inborn; the frequency of hyperglycaemia was similar for inborn (n/N=5/11; 45%) and outborn (n/N=12/31; 39%) neonates. The glucose profiles per hour in normoglycaemic v. hyperglycaemic neonates are shown in Fig. 1. The highest blood glucose levels occurred in the second and third hours of life, but hyperglycaemia was most frequent between the 5th and 7th hours of life. The maternal characteristics were similar in those with and without hyperglycaemia. None of the mothers smoked and drug/alcohol use was uncommon. There was no documented maternal infection, pyrexial illness or chorioamnionitis, nor antenatal bleeding. Intrapartum complications occurred in >50% of neonates and were similar between normoglycaemic and hyperglycaemic neonates; meconium-stained liquor was the most frequent complication, while sentinel events occurred in only one-fifth. Hyperglycaemia was associated with a lower 5-minute Apgar score (p=0.007), an increased frequency of severely abnormal aEEG at age 6 hours (p=0.029), and a higher Thompson HIE score at age 6 hours (p=0.002). There were no significant differences in the other characteristics between the two groups.

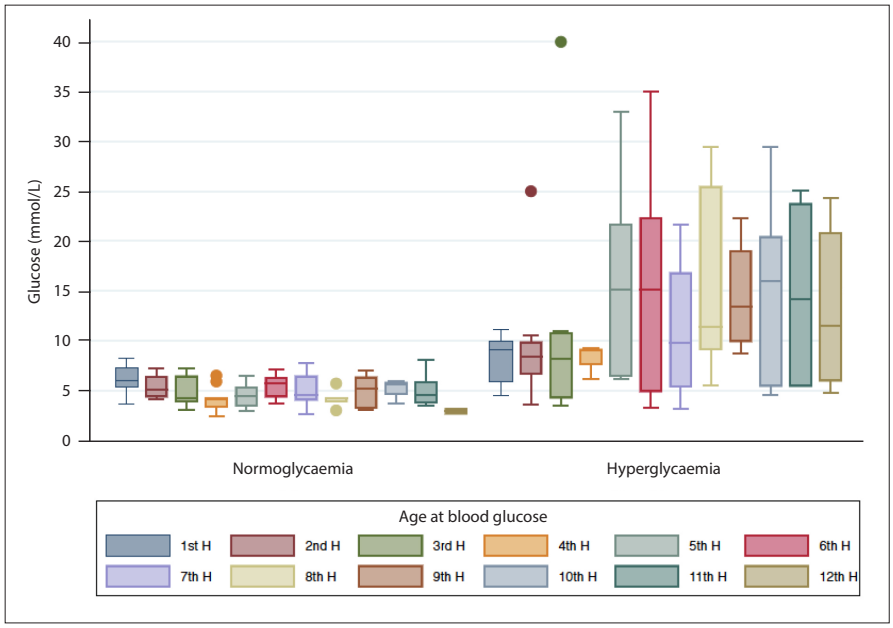

Fig. 1. Box plot comparing glucose profiles per hour in normoglycaemic v. hyperglycaemic neonates.

Neonatal morbidity during cooling and outcomes

Neonatal morbidity during cooling and outcomes are shown in Table 2. There were no significant differences in morbidity or neurological outcomes between the groups; however, mechanical ventilation and seizures occurred in double the proportion of neonates with hyperglycaemia compared with those who were normoglycaemic.

Five of the six neonates who died had hyperglycaemia; this was a significant finding with logistic regression, despite the wide confidence interval (CI) (OR 10; 95% CI 1 - 96; p=0.045), but inclusion of the 5-minute Apgar score in a multivariate regression model resulted in loss of independent association between hyperglycaemia and death (Table 3). The median (IQR) highest blood glucose concentration was three times higher in the neonates who died compared with those who survived; 21.3 (10.5 - 29.4) v. 7.2 (5.9 - 9.3) mmol/L (p=0.025), respectively. The distribution of highest blood glucose values according to mortality is shown in Fig. 2. Three of the four outliers in the 'survived' group were outborn and two of those three had a poor outcome with a severely abnormal aEEG at 48 hours. The inborn neonate had a normal aEEG at 6 and 48 hours. The highest blood glucose readings in the two with a normal short-term outcome was less than the 75% quartile of those who died.

There were no differences in the proportions of hyperglycaemic and normoglycaemic neonates with poor outcomes. There were also no differences in the median (interquartile range) highest blood glucose levels in those with poor v. normal outcomes; 8.1 (6.2 - 25.6) v. 7.2 (5.8 - 9.3) mmol/L, respectively. However, ROC analysis showed increasing specificity for a poor outcome with increasing blood glucose (Fig. 3). The sensitivity, specificity, ORs and likelihood ratios of any hyperglycaemia (blood glucose ≥8.4 mmol/L) and blood glucose levels that were associated with the highest proportion of correctly classified neonates per glucose cut-off level for poor v. normal short-term outcome, are shown in Table 4. The Stata's DIAGT module was used to determine CIs. The maximum blood glucose levels of ≥22.9 and ≥25.6 mmol/L had low sensitivities but high specificities for poor outcome (Table 4); however, the positive likelihood ratio was only significant at the cut-off point of 25.6 mmol/L. When

Table 1. Maternal and neonatal characteristics

Variable	Whole cohort (*N*=47), *n* (%) *	Hypoglycaemia (*n*=5), *n* (%) *	Normoglycaemia (*n*=25), *n* (%)*	Hyperglycaemia (*n*=17), *n* (%)*	*p*-value§
Maternal characteristics					
Age in years‡	24.5 (20 - 31.5)	27 (32 - 72)	24 (19 - 32.5)	25 (22 - 30.5)	0.51
Gravidity‡	2 (1 - 3)	2 (2 - 2)	2 (1 - 3)	1(1 - 3)	0.78
Illicit drug/alcohol use	2 (4)	0	1 (4)	1 (6)	1.00
Pre-eclampsia	4 (9)	2 (40)	1 (4)	1 (6)	1.00
Diabetes	6 (13)	1 (20)	2 (8)	3 (18)	0.38
Maternal seizures	4 (9)	2 (40)	0	2 (12)	0.16
Intrapartum complications	26 (55)	2 (40)	15 (60)	9 (53)	0.65
Prolonged ROM >18 hours	1 (2)	0	1 (4)	0	1.00
Sentinel event	10 (21)	1 (20)	5 (20)	4 (24)	1.00
Meconium-stained liquor	18 (38)	4 (80)	8 (32)	6 (35)	1.00
Abnormal or non-reassuring FHR	12 (26)	3 (60)	6 (24)	3 (18)	0.72
Prolonged second stage	11 (23)	0	7 (28)	4 (24)	1.00
Neonatal characteristics					
Highest glucose within first 12 hours‡	7.2 (5.8 - 10.5)	7.1 (5.5 - 7.4)	6.2 (5.3 - 7.1)	13.4 (9.9 - 25)	< 0.001
Outborn	32 (68)	1 (20)	19 (76)	12 (71)	0.73
Male	28 (60)	3(60)	16 (64)	9 (53)	0.47
Birthweight†	3 143 (596)	2 903 (896)	3 196 (518)	3 137 (629)	0.74
Cord/blood gas done within first hour	44 (93)	5 (100)	22 (88)	17 (100)	0.26
Highest base deficit (mmol/L) within first hour†	16.3 (7)	15 (6.9)	16.3 (6.2)	16.7 (8.6)	0.88
Highest lactate (mmol/L) within first hour†	9.6 (4)	10.8 (4.5)	8.7 (3.2)	10.1 (4.0)	0.25
Chest compressions at birth	10 (21)	1 (20)	5 (20)	4 (24)	1.00
Adrenaline at birth	5 (10)	0	3 (12)	2 (12)	1.00
5-min Apgar‡	5 (4 - 7)	6(5 - 6)	6 (5 - 7)	4 (3 - 5)	0.01
Sepsis risk	1 (2)	0	1 (4)	0 (0)	1.00
Abnormal aEEG pattern at 6 hours	21 (44)	1 (20)	9 (36)	11 (65)	0.07
Severely abnormal aEEG at 6 hours	18 (38)	0	8 (32)	10 (59)	0.03
Thompson HIE score at 6 hours‡	8 (5 - 11)	7 (5 - 9)	7 (5 - 8)	11 (8 - 14)	<0.001
Severe encephalopathy at 6 hours (modified Sarnat)	10 (21)	0	3 (12)	7 (41)	0.062
Cooled with gel-bag method	38 (80)	3 (60)	20 (80)	15 (88)	0.68
Age at initiation of cooling in hours†	3.8 (1.8)	2.6 (2.3)	4.2 (1.4)	3.6 (2)	0.25

CTG = cardiotocograph; IQR = interquartile range; SD = standard deviation; ROM = rupture of membranes; FHR = fetal heart rate; aEEG = amplitude-integrated electroencephalogram; HIE = hypoxic-ischaemic encephalopathy.
*Unless otherwise specified.
†Mean (SD).
‡Median (interquartile range).
§*p*-value refers to normoglycaemia v. hyperglycaemia.

Table 2. Neonatal morbidity during cooling and outcomes

Variable	Whole cohort (*N*=47), *n* (%)*	Hypoglycaemia (*n*=5), *n* (%)*	Normoglycaemia (*n*=25), *n* (%)*	Hyperglycaemia (*n*=17), *n* (%)*	*p*-value†
Morbidity					
Hypotension	7 (14)	1 (20)	4 (16)	2 (12)	1.00
Abnormal renal function‡	2 (4)	0	1 (4)	1 (6)	1.00
Pulmonary hypertension	4 (8.5)	1 (20)	2 (8)	1 (6)	1.00
Mechanical ventilation	17 (36)	1 (20)	7 (28)	9 (53)	0.10
Late-onset sepsis	2 (4)	0	0	2 (12)	0.16
Necrotising enterocolitis	1 (2)	0	1 (4)	0	1.00
Seizures	21 (45)	3 (60)	8 (32)	10 (59)	0.09
Outcomes					
Severely abnormal aEEG at 48 hours, *n/N* (%)	12/46 (27)	0	7 (28)	5/16 (31)	1.00
Mortality	6 (13)	0	1 (4)	5 (29)	0.03
Death or severely abnormal 48-hour aEEG	13 (28)	0	7 (28)	6 (35)	0.62

aEEG = amplitude-integrated electroencephalogram.
*Unless otherwise specified.
†*p*-value for normoglycaemia v. hyperglycaemia.
‡Serum creatinine >115 mmol/L.

Table 3. Logistic regression: Glycaemic profile and mortality

Parameter	Cohort (*N*=42), *n**	Alive (*n*=36), *n* (%)*	Died (*n*=6), *n* (%)*	OR (95% CI)	OR *p*-value	aOR (95% CI)	aOR *p*-value
Hyperglycaemia				10 (1 - 96)	0.045	5.9 (0.5 - 66)	0.15
Yes	17	12 (71)	5 (29)				
No	25	24 (96)	1 (4)				
5-minute Apgar, median (IQR)	5 (4 - 7)	6 (4 - 7)	4 (3 - 5)	0.6 (0.4 - 1)†	0.052	0.7 (0.4 - 1.2)†	0.22

OR = odds ratio; CI = confidence interval; aOR = adjusted odds ration; IQR = interquartile range.
*Unless otherwise specified.
†Change in OR per unit increase in 5-minute Apgar score.

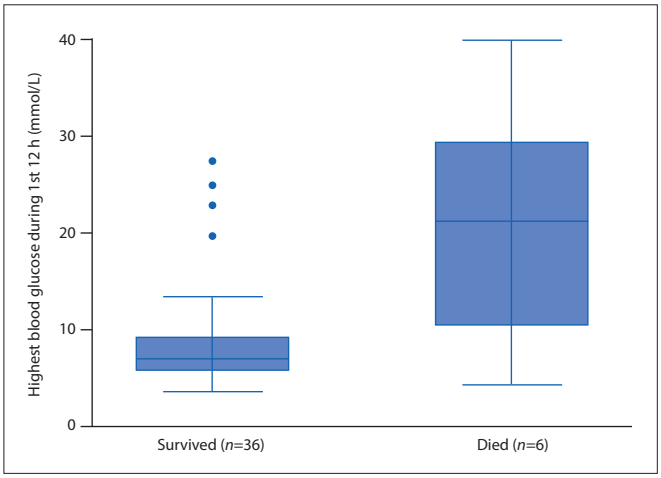

Fig. 2. Box plot comparing highest blood glucose with mortality.

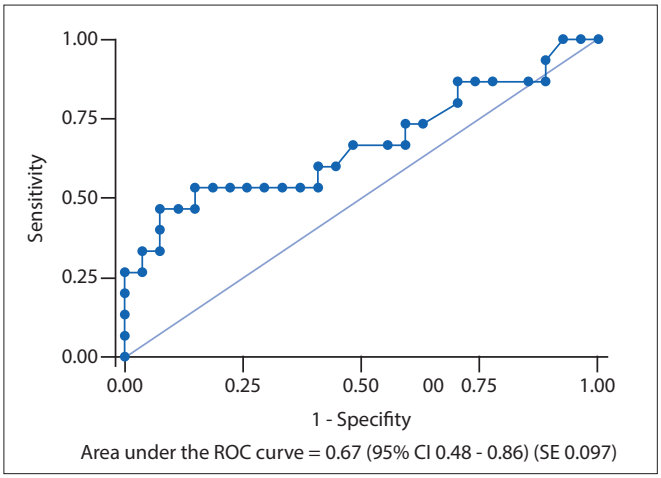

Fig. 3. Receiver operating curve (ROC) showing highest blood glucose v. poor outcome.

the 5-minute Apgar was included in logistic regression analysis with generalised linear modelling, the blood glucose level of ≥25.6 mmol/L remained independently associated with poor outcome with an adjusted incidence rate ratio (aIRR) of 3.5 (95% CI 1.5 - 8.4; *p*=0.005) (Table 5).

Discussion

We described early glucose profiles in the first 12 hours of life in a cohort of cooled neonates with moderate-to-severe HIE. Hypoglycaemia <2.3 mmol/L occurred in only 10% of the cohort and affected predominantly in-born neonates, none of whom had a poor outcome. The outcomes of neonates with hyperglycaemia v. normoglycaemia was the main focus of this study; both of which occurred in similar proportions of in- and out-born neonates.

Early hyperglycaemia >8.3 mmol/L during the first 12 hours of life, occurred in 36% of cooled neonates with moderate-severe HIE and was associated with 10-times higher odds of death than normoglycaemic neonates; however the association was not independent of the 5-minute Apgar score. The combined outcome of death or severely abnormal aEEG at 48 hours was only independently associated with early hyperglycaemia when blood glucose was ≥25.6 mmol/L.

The reason for the increased frequency of hypoglycaemia in inborn neonates was not apparent and the number of affected infants was too small to explore this finding further. The aetiology and pathogenesis of deranged glycaemic control in HIE is likely multi-factorial and the role of glucose homoeostasis as a biomarker of underlying pathological processes or as an immediate contributor to neuronal injury is not clearly defined.[11] The associations we found between hyperglycaemia and adverse short-term outcome are consistent with the findings of several studies of neonates with moderate-severe HIE.[9-11,18-20] Hyperglycaemia (>8.3 mmol/L) in the first 12 hours was independently associated with adverse outcome in two studies including both cooled and normothermic neonates with moderate-to-severe HIE.[10,11] Chouthai *et al.*[20] described a similar association with blood glucose levels >11.1 mmol/L during the first 24 hours in cooled neonates, and studies utilising continuous glucose monitoring in similar neonates have shown increased adverse outcomes proportionate to the extent and duration of hyperglycaemia during the first 3 days.[19]

Despite similar maternal and intrapartum characteristics, neonates with early hyperglycaemia in our study had significantly lower 5-minute Apgar scores and an increased frequency and severity of both encephalopathy and aEEG abnormalities. These findings suggest that hyperglycaemia may therefore serve as a proxy for severity of brain injury.[9] Hyperglycaemia following asphyxia in animal studies is thought to occur because of prolonged elevation of stress hormones with subsequent cell damage and neuronal apoptosis.[8] Despite showing an association between hyperglycaemia and adverse outcome, Basu *et al.*[9] found that early hyperglycaemia predicted an increased likelihood of response to hypothermia; they speculated that in some neonates early hyperglycaemia may occur after intense acute injury associated with sentinel events and therefore represents evolving brain injury that is more likely to be within the therapeutic window of hypothermia. While sentinel events have been associated with more severe brain injury and increased adverse outcome in several other studies of neonates treated with hypothermia, the relationship between sentinel events and hyperglycaemia was not documented and the improved therapeutic effect of cooling in this group was not consistently described.[21-23]

Contrary to the observations of Basu *et al.*,[9] we did not find an increased frequency of sentinel events in neonates with early

Table 4. Prediction of poor outcome: Highest blood glucose in the first 12 hours of life

Cutpoint (mmol/L)	Yes/No (*n*)	Poor outcome, *n* (row %)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Correctly classified (%)	OR (95% CI)	LR+ (95% CI)	LR– (95% CI)
≥8.4	Yes (17)	6 (35)	46 (19 - 75)	62 (42 - 79)	62	1.4 (0.4 - 5.1)	1.2 (0.6 - 2.6)	0.9 (0.5 - 1.6)
	No (25)	7 (28)						
≥10.5	Yes (12)	6 (50)	46 (19 - 75)	79 (60 - 92)	74	3.3 (0.8 - 13.1)	2.2 (0.9 - 5.6)	0.7 (0.4 - 1.2)
	No (30)	7 (23)						
≥13.4	Yes (9)	5 (56)	39 (14 - 68)	86 (68 - 96)	76	3.9 (0.9 - 17.1)	2.8 (0.9 - 8.7)	0.7 (0.5 - 1.1)
	No 33	8 (24)						
≥22.9	Yes (6)	4 (67)	31 (9 - 61)	93 (77 - 99)	74	6.0 (1.1 - 32.9)	4.5 (0.9 - 21.4)	0.7 (0.5 - 1.1)
	No (36)	9 (25)						
≥25.6	Yes (4)	4 (100)	31 (9 - 61)	100 (88 -100)	71	28.0* (1.4 - 568.0)	19.3* (1.1-334)	0.7 (0.5 - 1.0)
	No (38)	9 (24)						

CI = confidence interval; OR = odds ratio; LR+ = positive likelihood ratio; LR- = negative likelihood ratio.
*When zero-count cells are present, 0.5 is added to all cell frequencies before calculation.

Table 5. Logistic regression with severe hyperglycemia and poor outcome

Parameter	Cohort (*N*=42)		Poor outcome (*n*=36), *n* (%)*	Normal (*n*=6)	IRR (95% CI)	IRR *p*-value	aIRR (95% CI)	aIRR *p*-value
Blood glucose ≥25.6 mmol/L	Yes	4	4 (100)	0	4.2 (2.4 - 7.5)	<0.001	3.5 (1.5 - 8.4)	0.01
	No	38	9 (24)	29 (76)				
5-minute Apgar, median (IQR)		5 (4 - 7)	5 (3 - 5)	6 (4 - 7)	0.8 (0.7 - 1)†	0.015	0.9 (0.1 - 1.1)†	0.57

IRR = incidence rate ratio; aIRR = adjusted incidence rate ratio; IQR = interquartile range.
*Unless otherwise specified.
†Change in IRR per unit increase in 5-minute Apgar score.

hyperglycaemia. The likely multifactorial causality of neonatal hyperglycaemia and hence variable pathophysiology is further supported by a recent MRI study where brain injury in neonates with hyperglycaemia was not limited to the basal ganglia and thalamus but was also seen in the anterior and posterior white matter, the corpus callosum, the posterior limb of the internal capsule, and the optic radiations.[20]

The lower Apgar scores and increased aEEG severity prior to cooling in our hyperglycaemic group contrasts with the subsequent finding of similar proportions of hyperglycaemic and normoglycaemic neonates with severely abnormal aEEG at 48 hours. We speculate this finding may indicate a response to cooling in survivors, since hypothermia has a greater therapeutic effect on disability than survival;[2] however poor outcome still occurred in 35% and the sample was too small to measure this effect.

The low sensitivity of hyperglycaemia for an abnormal outcome is in keeping with the several other potential causes of poor outcome – severe hyperglycaemia is not the only cause of poor outcome and is not associated with all other causes of poor outcome. A test with high specificity indicates that if the test is positive, the associated outcome is highly likely so it can be used to make decisions based on that outcome; the associated low sensitivity indicates that a negative test (the absence of severe hyperglycaemia) does not exclude a poor outcome.

The use of hyperglycaemia to predict response to cooling is problematic because hyperglycaemia may independently cause cellular injury which may be exacerbated during or after hypoxic ischaemia and this is supported by the finding that hyperglycaemia has been independently and temporarily associated with aEEG abnormalities.[24] The survival with normal short-term outcome in two of the four neonates who survived despite being outliers, may be related to having lower maximum blood glucose, a better response to cooling, or genetic factors. In addition, a dose-response relationship between hyperglycaemia and adverse outcome in babies with HIE has been described and hyperglycaemia can be independently caused by hypothermia and/or iatrogenic glucose administration.[19,20]

Study limitations and stengths

Firstly, the retrospective nature of the study may have compromised the accuracy of findings. Secondly, the small sample size decreases the confidence in the findings. Finally, the use of severely abnormal aEEG at 48 hours as a proxy for poor outcome is not absolute and long-term neurodevelopmental outcomes may differ. The strengths of the study include the uniform management of the neonates following standard guidelines, the high proportion of neonates with early blood gases and the inclusion of objective aEEG data.

Conclusion

Hyperglycaemia was common in the first 12 hours of life in cooled neonates with moderate-to-severe HIE, and it was associated with increased illness severity at birth and death despite cooling. Only severe hyperglycaemia (≥25.6 mmol/L) was associated with the combined outcome of death/severely abnormal aEEG at 48 hours. Our data do not support the use of early hyperglycaemia as an indicator to select neonates for therapeutic hypothermia. Further studies comparing glucose management and outcome are needed to explore the potential beneficial effect(s) of improved glucose control on outcome.

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MS developed the protocol, extracted and analysed some of the data and wrote the manuscript under the supervision of SP, MCH and ARH; SP assisted with protocol design and supervised as above; VN contributed substantially to data acquisition and interpretation; MCH assisted with protocol design and supervised as above; ARH had overall oversight of the research, assisted with protocol design and data analysis and supervised as above.

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