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Hypoglycaemia and hyperglycaemia are associated with unfavourable outcome in infants with hypoxic ischaemic encephalopathy: A post hoc analysis of the CoolCap Study

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Group information: The members of the CoolCap Study Group and other collaborators are listed at the end of the article.

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Short title: Deranged glucose is associated with poor outcome in HIE

Abbreviations: HIE – hypoxic ischaemic encephalopathy; ATP – adenosine triphosphate

Key words: hypoglycaemia, hyperglycaemia, neonatal, hypoxic, encephalopathy, CoolCap, unfavourable outcome

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What is already known on this topic

- Postnatal deranged glucose homeostasis is common in infants with hypoxic ischaemic encephalopathy; the relationship with long-term outcome is unclear.

- Previous studies have found univariable associations with hypoglycaemia and hyperglycaemia and long-term outcome, but not after multivariable analysis.

What this study adds

- This study reports that hypoglycaemia and hyperglycaemia during the early postnatal period in infants with hypoxic ischaemic encephalopathy are associated with unfavourable outcome at 18 months.

- These associations remained significant after adjusting for birth weight, Apgar score, pH, Sarnat stage, and hypothermia therapy.

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- The odds of an unfavourable outcome were higher in infants with hypoglycaemia (OR=6.2), hyperglycaemia (OR=2.7), and any glucose derangement (OR=3) compared with normoglycaemic infants.

ABSTRACT

Objective: To investigate the association of neonatal hypoglycaemia and hyperglycaemia with outcomes in infants with hypoxic ischaemic encephalopathy (HIE).
Design: Post hoc analysis of the CoolCap Study.
Setting: 25 perinatal centres in UK, USA, and New Zealand during 1999–2002.
Patients: 234 infants at ≥36 weeks' gestation with moderate-to-severe HIE enrolled in the CoolCap Study. 214 (91%) infants had documented plasma glucose and follow-up outcome data.
Intervention: Infants were randomised to head cooling for 72 hours starting within 6 hours of birth, or standard care. Plasma glucose levels were measured at pre-determined time intervals after randomisation.
Main outcome measure: The unfavourable primary outcome of the study was death and/or severe neurodevelopmental disability at 18 months. Hypoglycaemia (≤40 mg/dL, ≤2.2 mmol/L) and hyperglycaemia (>150 mg/dL, >8.3 mmol/L) during the first 12 hours after randomisation were investigated for univariable and multivariable associations with unfavourable primary outcome.
Results: 121 (57%) infants had abnormal plasma glucose values within 12 hours of randomization. Unfavourable outcome was observed in 126 (60%) infants, and was more common among subjects with hypoglycaemia (81%, p=0.004), hyperglycaemia (67%, p=0.01), and any glucose derangement within the first 12 hours (67%, p=0.002) compared with normoglycaemic infants (48%) in univariable analysis. These associations remained significant after adjusting for birth weight, Apgar score, pH, Sarnat stage, and hypothermia therapy.
Conclusions: Both hypoglycaemia and hyperglycaemia in infants with moderate-to-severe HIE were independently associated with unfavourable outcome. Future studies are needed to investigate the prognostic significance of these associations and their role as biomarkers of brain injury.

INTRODUCTION

Hypoxic ischaemic encephalopathy (HIE) is one of the most serious perinatal complications, and remains associated with a high risk of death or long-term neurodisability. Despite advances in obstetric care, moderate-to-severe HIE affects 1.5–3 per 1000 term live births in developed countries.[1, 2] There is now compelling evidence that mild hypothermia induced within 6 hours after resuscitation can improve long-term survival without disability.[3] However, many infants still die or survive with disability, and recent data suggest that longer or deeper cooling did not reduce death at hospital discharge.[4] Thus, it is important to investigate whether other factors may help to further optimize care.

Glucose is the primary substrate for energy metabolism in the newborn brain, and deranged metabolism may contribute to neuronal injury.[5, 6] At birth, the continuous transplacental infusion of glucose ends; normal postnatal glucose homeostasis then depends on hepatic glycogen reserves, hormonal regulation, and external provision of enteral or parenteral substrate. Hypoglycaemia and hyperglycaemia occur frequently in infants with HIE, likely due to the profound metabolic and hormonal disturbances.[7-9] Their effect on long-term outcome is unclear. Although one study found that early hypoglycaemia was a risk factor for short-term perinatal brain injury in newborns with HIE,[9] others did not find a relationship between early hypoglycaemia and adverse neurodevelopmental outcome at 24 months age after adjusting for HIE severity.[7] Two retrospective studies reported conflicting results on the association

between early hyperglycaemia and unfavourable outcome in infants with HIE.[7, 10] Thus, there is no conclusive evidence that deranged glucose metabolism in infants with HIE is independently associated with unfavourable long-term neurologic outcome.

Animal studies support the potential for neuronal injury from deranged glucose homeostasis in the setting of asphyxia. Induced hypoglycaemia decreased the cerebrovascular response to hypoxia, increased cerebral superoxide production and aspartate levels in the brain extracellular space, and promoted neuronal necrosis.[11-14] Hyperglycaemia before acute hypoxia-ischaemia or ischaemia markedly increased brain injury in animal models.[15-17]

We therefore examined the hypothesis that early transient or recurrent hypoglycaemia (≤40 mg/dL, ≤2.2 mmol/L)[8] and hyperglycaemia (>150 mg/dL, 8.3 mmol/L)[7] in infants with moderate-to-severe HIE would be independently associated with death or severe neurodevelopmental disability (primary unfavourable outcome) in a post-hoc analysis from the CoolCap Study.[18]

METHODS

Subjects

The CoolCap Study was a multicentre randomised controlled study of selective head cooling and mild systemic hypothermia for the treatment of perinatal moderate-to-severe HIE in 234 infants at ≥36 weeks' gestation enrolled between 1999 to 2002.[18] This study was performed in 25 perinatal centres using a trial design registered with the US Food and Drug Administration under the Investigational Device Exemption/Premarket Approval program. The institutional review board at each centre approved the protocol, and written informed consent was obtained from parents before randomization. Study subjects were randomised to head cooling for 72 hours starting within 6 hours of birth, with rectal temperature maintained at 34.5±0.5°C, followed by rewarming over 4 hours, or standard care at 37.0±0.5°C. The primary unfavourable study outcome was death or severe disability (i.e., Gross motor function classification system level 3–5, Bayley scales of infant development II mental developmental index <70, or bilateral cortical visual impairment) at 18 months. CoolCap Study subjects were eligible (n=215, 92 %) for the current analysis if they completed follow-up evaluations and plasma glucose values were available in the database (figure 1).

Plasma glucose levels, at pre-defined time points (0, 4, 8, 12, 24, 48, and 72 hours from randomisation) were analysed to investigate the association between derangements in glucose homeostasis with the primary unfavourable outcome. Demographic and perinatal data, included birth weight, gestational age, gender, race, mode of delivery, pregnancy complications, and Apgar scores at 1 and 5 minutes. Other clinical data were first pH, modified Sarnat and Sarnat stage at randomisation,[19] age at study randomisation, treatment with hypothermia or conventional therapy, presence of seizures, death, and Bayley Scales of Infant Development II

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mental developmental index scores at 18 months. Infants were randomised at a median of 4.8 (IQR: 4.1–5.3) hours after birth in the CoolCap Study. For the purposes of this study, time points refer to the period after randomisation, and not hours of life.[18]

Statistical analysis

Demographic, obstetric, and neonatal parameters were stratified by primary outcome (favourable vs unfavourable) and compared using chi-square test, Fisher's exact test, t-test, or Wilcoxon rank sum test as appropriate. Episodes of hypoglycaemia, normoglycaemia, and hyperglycaemia as single or recurrent occurrences during the first 12 hours were documented for all subjects. Multiple logistic regression models were built to investigate the association between deranged glucose values and an unfavourable outcome. Covariates with $p<0.1$ from univariable analysis were included *a priori* in the multiple regression models. Statistical significance for the final models was assessed at the 0.05 level, and no adjustment was made for multiple hypothesis testing in this exploratory analysis. Statistical analysis was conducted using Stata version 12.1 (StataCorp LP, College Station, TX USA, 2011).

RESULTS

Study demographic data stratified by 18-month outcome are shown in table 1. Infants with an unfavourable outcome were generally larger, less likely to have been cooled, had more severe vs. moderate HIE, had lower 5-minute Apgar scores, and were more acidotic. Incidentally, only 4 study infants had septicaemia. Therefore, meaningful statistical associations between septicaemia and glucose derangements and outcome could not be established.

Table 1 Baseline characteristics of infants from the CoolCap Study

Characteristics n (%)	All subjects	Favourable outcome	Unfavourable outcome	p Value
	215	85 (39.5%)	130 (60.5%)	
Birth weight, mean (SD), g	3445 (646)	3295 (625)	3544 (643)	0.006
Hypothermia treatment, n (%)	107 (50%)	49 (58%)	58 (45%)	0.06
Severe HIE, n (%)	74 (35%)	15 (18%)	59 (46%)	<0.001
Male, n (%)	114 (53%)	44 (52%)	70 (54%)	0.77
Caesarean delivery, n (%)	149 (69%)	64 (75%)	85 (65%)	0.12
Delivery complications[*], n (%)	174 (81%)	66 (78%)	108 (83%)	0.32
White race, n (%)	136 (63%)	54 (64%)	82 (63%)	0.95
Apgar 5 minutes, median [IQR]	3 [0–4]	3 [1–4]	2 [0–4]	0.02
pH, mean (SD)	6.88 (0.22)	6.95 (0.22)	6.83 (0.21)	<0.001

*Delivery complications include prolapsed cord, true knot in the cord, umbilical cord tear, shoulder dystocia, placental abruption, feto-maternal bleeding, ruptured uterus, antepartum haemorrhage, traumatic instrument delivery, head entrapment, and others.

Early postnatal glucose profile

The time period after randomisation that was most informative for predicting an unfavourable outcome was during the first 12 hours. At the time of randomisation, of infants with recorded plasma glucose levels, 7% (15/205) were hypoglycaemic and 34% (70/205) were hyperglycaemic. During the first 12 hours, 13% (27/214) of infants had at least one episode of

hypoglycaemia, 48% (102/214) had at least one episode of hyperglycaemia, and 57% (121/214)

had ≥1 episode(s) of hypoglycaemia or hyperglycaemia (table 2). Of 207 infants who had ≥1

glucose values obtained during the first 12 hours, 30% had ≥2 deranged values and 8% had both

hypoglycaemia and hyperglycaemia. The incidence of hypoglycaemia and hyperglycaemia

progressively decreased over time during the 72-hour study period. Later (>12 hours after

randomisation) glucose derangements were not associated with outcome.

Table 2 Univariable analysis of association of deranged glucose parameters with unfavourable
outcome

Deranged glucose parameter within first 12 hours after randomisation	*n*	Infants with deranged glucose *n* (%)	Unfavourable outcome among infants with deranged glucose (%)	Unfavourable outcome among normoglycaemic infants (%)	p Value
Hypoglycaemia	214[a]	27 (13)	22/27 (81)	45/93 (48)	0.004
Hyperglycaemia	214	102 (48)	68/102 (67)	45/93 (48)	0.01
Hypoglycaemia and/or hyperglycaemia	214	121 (57)	84/121 (69)	45/93 (48)	0.002
Both hypoglycaemia and hyperglycaemia	207[b]	8 (4)	6/8 (75)	42/88 (48)	0.27
Recurrent hypoglycaemia	207	11 (5)	9/11 (82)	42/88 (48)	0.052
Recurrent hyperglycaemia	207	39 (19)	30/39 (77)	42/88 (48)	0.002
Recurrent hyperglycaemia or hypoglycaemia	207	63 (30)	50/63 (79)	42/88 (48)	<0.001

[a]1 infant did not have any documented glucose within first 12 hours.
[b]7 infants had only single glucose values within the first 12 hours.

Univariable analysis

Relationship between deranged glucose at individual time points (0, 4, 8, and 12 hours) and

unfavourable outcome

At the time of randomisation, 9% and 41% of infants with unfavourable outcome had hypoglycaemia or hyperglycaemia, respectively, compared to 5% and 24% of infants with favourable outcome (p=0.011). Derangements of glucose at 4 and 8 hours were significantly more common in infants with unfavourable outcome (figure 2).

Relationship between hypoglycaemia within 12 hours and unfavourable outcome

Infants with at least one episode of hypoglycaemia during the first 12 hours were more likely to have an unfavourable outcome. Among the 27 infants with hypoglycaemia within 12 hours, 22 (81%) had an unfavourable outcome at 18 months of age compared to only 48% of infants with normoglycaemia (p=0.004, table 2).

Relationship between hyperglycaemia within 12 hours and unfavourable outcome

Infants with at least one episode of hyperglycaemia during the first 12 hours were also more likely to have an unfavourable outcome. Among the 102 infants with hyperglycaemia within 12 hours, 68 (67%) had an unfavourable outcome, significantly higher than normoglycaemic infants (p=0.01, table 2).

Relationship between recurrent glucose derangements and unfavourable outcome

Recurrent hypoglycaemia (>1 episode within the first 12 hours) was present in only 11 (5%) of the infants; 82% of these infants had an unfavourable outcome, compared to 48% among normoglycaemic infants (p=0.052, table 2). Recurrent hyperglycaemia (>1 episode within the first 12 hours) was noted in 19% (39/207) of the infants; 77% of these infants had an unfavourable outcome compared with 48% among infants with normoglycaemia (p=0.002, table 2).

Multivariable analysis

Glucose derangements were significant independent predictors of unfavourable outcome after adjusting for birth weight, hypothermia therapy, Sarnat stage (III vs II), Apgar score at 5 minutes, and first pH (table 3). The odds of an unfavourable outcome were 6.2 times greater among infants with at least one episode of hypoglycaemia, 2.7 times greater among infants with at least one episode of hyperglycaemia, and 3 times greater in those with at least one episode of any glucose derangement (hypoglycaemia or hyperglycaemia) within the first 12 hours compared to normoglycaemic infants. Infants with recurrent hypoglycaemia (5% of infants, OR=2.1, 95% CI 0.52 to 8.3) and recurrent hyperglycaemia (19% of infants, OR=4.5, 95% CI 1.7 to 12.0) had an increased incidence of unfavourable outcome (82% and 77%, respectively), although the number of newborns with recurrent glucose abnormalities was small.

Table 3 Multivariable analysis of association of deranged glucose parameters with unfavourable outcome

Deranged glucose parameter within 12 hours of randomisation	Unfavourable outcome		
	Adjusted OR	95% CI	p Value
Hypoglycaemia	6.2	1.4 to 27.3	0.016
Hyperglycaemia	2.7	1.5 to 4.9	0.001
Hypoglycaemia or hyperglycaemia	3.0	1.6 to 5.8	0.001
Both hypoglycaemia and hyperglycaemia	3.5	0.99 to 12.1	0.052
Recurrent hypoglycaemia	2.1	0.52 to 8.3	0.304
Recurrent hyperglycaemia	4.5	1.7 to 12.0	0.003
Recurrent hypoglycaemia and/or hyperglycaemia	2.5	1.4 to 4.2	0.001
Recurrent hyperglycaemia and/or hypoglycaemia	5.0	1.9 to 13.5	0.001

Statistical model adjusted for birth weight, hypothermia therapy, Sarnat stage (III vs II), Apgar score at 5 minutes, and first pH.

DISCUSSION

This study reports systematically collected and analysed evidence that early hypoglycaemia, hyperglycaemia, and indeed, any glucose derangement during the early postnatal period, in infants with moderate-to-severe HIE are independently associated with an unfavourable outcome at 18 months. It is not possible to determine from this exploratory analysis whether this association with deranged glucose metabolism is causal. Hypoglycaemia reflects at least in part depletion of hepatic glycogen reserves during severe asphyxia, and hepatic injury.[20] Similarly, hyperglycaemia may be a proxy for severity of brain injury, as severely damaged tissues show reduced net metabolism,[21] or due to prolonged elevation of stress hormones after asphyxia.[22] Consistent with the present study, neonatal hyperglycaemia is common in preterm and sick infants.[23] The specific mechanisms are likely multifactorial, related to impaired insulin response, excessive hepatic glucose production, sepsis, and stress-induced increase in counter-regulatory hormones.[24, 25]

Neonatal hypoglycaemia has been investigated for its association with unfavourable neurodevelopmental and academic outcome in term and preterm infants.[26-28] Although the definition of neonatal hypoglycaemia has been highly controversial, the American Academy of Pediatrics currently recommends early identification of the at-risk infant and institution of prophylactic measures to prevent neonatal hypoglycemia.[29] However, only a few studies have examined the influence of early hypoglycaemia in infants with HIE on long-term neurodevelopmental outcome.[7-9, 30] One study of 60 infants with HIE showed a significant association between hypoglycaemia and HIE severity, but did not evaluate longer-term outcomes.[9] In another study of 185 term infants with fetal acidemia, investigators observed that hypoglycaemia was associated with early abnormal neurologic outcome (i.e., severe HIE

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and death, moderate-to-severe HIE, and seizures). However, this study did not evaluate outcome after hospital discharge.[8] In another study, although early hypoglycaemia was associated with adverse outcome at 24 months in 52 term infants with HIE in univariate analysis, hypoglycaemia was not a significant predictor after adjustment for severity of HIE.[7] None of the infants included in the above studies received therapeutic hypothermia.[7-9] More recently, in a prospective cohort study of 94 term infants at risk for neonatal encephalopathy, of whom 12% were treated with hypothermia, investigators reported that hypoglycaemia was associated with worse motor and cognitive outcome at 1 year.[30]

There are very limited data describing hyperglycaemia in neonates outside of sick extremely premature infants or due to iatrogenic causes, and its relationship with outcome is not clearly understood.[23] A retrospective analysis of 52 term infants with HIE found that hyperglycaemia occurred frequently but was not associated with an unfavourable outcome.[7] Conversely, in a smaller retrospective study, early hyperglycaemia (in univariate analysis only) in infants with HIE was associated with long-term gross motor deficits.[10] We previously reported that mild hypothermia was associated with an early increase in mean plasma glucose levels.[18] The present study demonstrates that hypoglycaemia as well as hyperglycaemia during the first 12 hours were associated with an unfavourable outcome at 18 months age, independent of severity of HIE and cooling therapy.

Our findings are supported by pathophysiologic observations of deranged energy metabolism from animal models of asphyxia. During asphyxia, anaerobic glycolysis in the brain increased less in hypoglycaemic than normoglycaemic newborn dogs, resulting in more rapid exhaustion of high-energy phosphate reserves (phosphocreatine and ATP).[31] Hypoglycaemia selectively

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impairs cerebrovascular autoregulation by suppressing adenosine-mediated cerebrovascular dilation in newborn piglets.[11]

Hyperglycaemia during hypoxia-ischaemia or ischaemia increases subsequent brain injury in piglets, fetal sheep, and adult rodents.[15-17] In fetal sheep, hyperglycaemia during asphyxia reduces cerebral oxygen consumption and increases acidosis.[32] In contrast, post-insult treatment has had variable results. Some studies, in neonatal rodents, piglets, and fetal sheep have suggested no effect.[16, 33, 34] In contrast, in newborn piglets, hyperglycaemia impaired recovery of brain cell membrane function and energy metabolism. [35] Further, hyperglycaemia following maternal dexamethasone treatment after asphyxia in fetal sheep was associated with increased brain injury.[36] It may be that these contrasting results reflect more adverse effects of greater durations of hyperglycaemia, or a deleterious effect of the combination of high levels of glucocorticoids with hyperglycaemia. Finally, it is interesting to note that although glucose infusion after asphyxial cardiac arrest per se did not increase injury in adult rats, a combined glucose and insulin infusion markedly reduced histological brain injury.[37]

[18]F-fluorodeoxyglucose positron emission tomography imaging in infants with HIE has found deranged glucose metabolism in affected brain areas.[38] Total and regional cerebral glucose metabolic rates measured during the subacute period after perinatal asphyxia in term infants was inversely correlated with HIE severity and short-term outcome.[39] Magnetic resonance imaging on day 3 in infants with HIE and hypoglycaemia suggests that hypoglycaemic brain injury was superimposed on patterns of hypoxic ischaemic brain injury.[40]

Several limitations of the present study should be taken into consideration. The analysis was post hoc, and so it is important that the findings are confirmed in prospective studies. We do not have glucose values between the pre-defined time points or continuous values and so may have

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underestimated the true incidence and duration of hypoglycaemia and hyperglycaemia. However, the study is strengthened by the regular and systematic determination of glucose levels at discrete time points that were not dependent on clinical decisions as in other retrospective studies. Glucose infusion rates from parenteral nutrition and intravenous fluids were not standardized across subjects, and this information was not available for the present exploratory analysis. Further, there was no information regarding treatment thresholds or interventions used, as this was not pre-specified by the original study, whether interventions were provided, or how interventions to achieve normoglycaemia influenced outcome. Thus, the trend of glucose levels towards normoglycaemia over time could represent a response to treatment or more likely, the natural history of improving glucose homeostasis in infants with moderate-to-severe HIE. We also do not have information on the source (arterial, venous, or capillary) of blood samples, and whether different sources of glucose levels could affect interpretation. Future prospective studies are needed to further investigate these associations.

CONCLUSIONS

Deranged glucose homeostasis was common during the first 12 hours after randomisation in infants with moderate-to-severe HIE. Both hypoglycaemia and hyperglycaemia were associated with unfavourable outcome at 18 months of age, independent of HIE severity and hypothermia treatment. Future studies are needed to investigate whether early deranged glucose metabolism in infants with HIE is a biomarker for neuronal injury, has prognostic significance, and aggravates further brain injury.

Acknowledgements

Contributors

SKB: conceptualized and designed the study, drafted the initial manuscript, and approved the final manuscript as submitted. JRK, RG, and AJG: conceptualized and designed the study, supervised data analysis and interpretation, reviewed and revised the manuscript, and approved the final manuscript as submitted. CGM and DG: performed data analysis, summarized results, critically reviewed the manuscript, and approved the final manuscript as submitted.
All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Figure legends

Figure 1 Flow of infants through the trial

Figure 2 Distribution of glucose values at each time point during the first 12 hours stratified by favourable vs unfavourable primary outcome

Caption: Y-axis depicts percentage of subjects with hyperglycaemia, normoglycaemia, and hypoglycaemia at each time point. The n is reported in the columns.

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Infants assessed for eligibility (n=541)

Excluded (n= 307)
• Not meeting inclusion criteria (n= 271)
• Declined to participate (n=15)

Randomized in CoolCap Study (n= 234)

Randomized to head cooling (n= 116)
• Received head cooling intervention (n=112)
• Not cooled (n= 4)

Randomized to conventional care (n= 118)
• 1 cooled briefly

Lost to follow-up

Lost to follow-up

Glucose data unavailable

Glucose data unavailable

215 infants included for post hoc analysis

1 infant had no glucose data within first 12

214 infants included for univariable analysis

4 infants had missing Sarnat

210 infants included for multivariable analysis