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An emerging evidence base for the management of neonatal hypoglycaemia

Jane E Harding [a,*], Deborah L Harris [a,b], Joanne E Hegarty [a,c], Jane M Alsweiler [a,c,d], Christopher JD McKinlay [a,d,e]

[a] Liggins Institute, University of Auckland, 85 Park Ave, Grafton, Auckland 1023, New Zealand
[b] Waikato Hospital, Selwyn Street and Pembroke Street, Hamilton 3204, New Zealand
[c] National Women's Health, Auckland City Hospital, 2 Park Rd, Grafton, Auckland 1023, New Zealand
[d] Department of Paediatrics: Child and Youth Health, University of Auckland, 2 Park Rd, Grafton, Auckland 1023, New Zealand
[e] Kidz First Neonatal Care, Counties Manukau Health, Private Bag 93311, Otahuhu, Auckland, New Zealand

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ABSTRACT

Neonatal hypoglycaemia is common, and screening and treatment of babies considered at risk is widespread, despite there being little reliable evidence upon which to base management decisions. Although there is now evidence about which babies are at greatest risk, the threshold for diagnosis, best approach to treatment and later outcomes all remain uncertain. Recent studies suggest that treatment with dextrose gel is safe and effective and may help support breast feeding. Thresholds for intervention require a wide margin of safety in light of information that babies with glycaemic instability and with low glucose concentrations may be associated with a higher risk of later higher order cognitive and learning problems. Randomised trials are urgently needed to inform optimal thresholds for intervention and appropriate treatment strategies.

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* Corresponding author.
E-mail addresses: j.harding@auckland.ac.nz (J.E. Harding), Deborah.Harris@waikatodhb.health.nz (D.L. Harris), jhegarty@adhb.govt.nz (J.E. Hegarty), j.alsweiler@auckland.ac.nz (J.M. Alsweiler), c.mckinlay@auckland.ac.nz (C.J.D. McKinlay).

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1. Introduction

Hypoglycaemia is the commonest metabolic disorder of the newborn, and perhaps the only readily preventable cause of neonatal brain injury. Despite this, management of neonatal hypoglycaemia has for decades been based on extremely limited evidence. This article outlines some current dilemmas in clinical management and describes some recent research that is beginning to indicate the potential for a more evidence-based approach to the diagnosis and treatment of neonatal hypoglycaemia.

2. Pathophysiology

Before birth the fetus receives a continuous intravenous supply of glucose, which crosses the placenta by carrier-mediated facilitated diffusion from the maternal circulation. During labour and delivery the secretion of stress hormones such as glucocorticoids and catecholamines causes a rise in fetal blood glucose concentrations, so that cord blood glucose concentrations are often high [1,2].

Once the umbilical cord is cut, the exogenous supply of glucose ceases, and blood glucose concentrations fall. This fall in blood glucose results in a decrease in insulin secretion and increase in counter-regulator hormones such as glucagon, catecholamines and glucocorticoids. Together, these changes initiate fetal endogenous glucose production via glycogenolysis and gluconeogenesis, with a resultant stabilisation of blood glucose concentrations, although adult concentrations are not reached until approximately 72 h of age [2,3].

Failure of this sequence of physiological changes can lead to hypoglycaemia, which is most common in the first few hours after birth. In the majority of babies this hypoglycaemia is transient, recovering over a few hours to days, and is usually termed transitional hypoglycaemia. In a smaller number of babies the hypoglycaemia persists for days to weeks, and a few of these will turn out to have persistent neonatal hyperinsulinism and require additional interventions. There is some evidence that even transitional hypoglycaemia is likely to be due to relative hyperinsulinaemia [4].

Although management of hypoglycaemia is largely focussed on managing blood glucose concentrations, it is important to remember that the real objective is to ameliorate the risk of brain injury. Glucose is the major fuel for the brain, and for a neonate with a relatively large brain, almost all of the estimated total body glucose consumption can be accounted for by the brain. Since brain glucose uptake is directly proportional to circulating concentrations, in the absence of alternative brain fuels, any reduction in blood glucose concentrations results in a reduction in available brain oxidative substrates. Persistent hyperinsulinaemia is therefore important, because it may limit the production of alternative cerebral fuels such as ketones that may be otherwise neuroprotective during hypoglycaemia.

3. Definition

The difficulty in agreeing a definition for neonatal hypoglycaemia is related to the continued uncertainty as to what is a normal blood glucose concentration and what may cause damage. Methods to define neonatal hypoglycaemia have included statistical [5], metabolic [3], neurophysical [6] and neurodevelopmental [7–9]. However, each of these methods is problematic. There are few studies of normal babies from which to extrapolate statistical definitions, especially in low risk exclusively breast fed babies [2]. Further, even if healthy term babies sometimes have low glucose concentrations during transition, it does not follow that their references ranges should be normative for infants at risk of impaired metabolic adaptation, many of whom have other risk factors for adverse development.

3.1. The 2.6 mM threshold

One definition in common use is <2.6 mM, which arose primarily from reports by Lucas et al. and Koh et al. in the 1980s. Koh et al. determined that in babies (n = 5) and children (n = 12) monitored during spontaneous and induced hypoglycaemia, abnormal sensory evoked potentials occurred only in those with blood glucose concentrations < 2.6 mM [6]. However, the onset of abnormal sensory evoked potentials occurred over a range of blood glucose concentrations (0.7 to 2.5 mM), suggesting that different individuals may have different levels of susceptibility. In six participants, sensory evoked potentials returned to normal following correction of hypoglycaemia, but the remaining four babies had delayed recovery (1 h to 16 days). The authors recognised that the abnormalities in evoked potential had not been shown to cause permanent damage, but surmised that they would not be of benefit, and advised that blood glucose concentrations be maintained above 2.6 mM.

In the same year, Lucas et al. demonstrated an association between repeated episodes of hypoglycaemia and reduced scores on the Bayley Infant Scales of Development at 18 months' corrected age [7]. They studied preterm babies (<1850 g) admitted to neonatal intensive care who had intermittent blood glucose concentration measurements. Bayley scores were regressed on days of hypoglycaemia, using blood glucose concentration cut-offs varying from 0.4 to 4 mM, and a significant association was seen using a cut-off of <2.5 mM. Lucas et al. therefore selected 2.6 mM as the cut off, and showed that hypoglycaemia on three or more days was significantly related to mental and motor developmental scores. Therefore, the authors advised that blood glucose concentrations be maintained above 2.6 mM [7]. A subsequent follow-up study demonstrated that the neurodevelopmental impairment persisted, with reduced scores for arithmetic and motor function [8].

Following publication of these two key studies, <2.6 mM has remained a common, though debated, definition of neonatal hypoglycaemia worldwide.

3.2. Different operational thresholds

There is uncertainty about whether it is necessary to correct low blood glucose concentrations in babies who have brief, early (1 to 2 h of age) low blood glucose concentrations and who are asymptomatic [10]. This uncertainty is due to the fall in blood glucose concentrations after birth which is commonly considered to be a normal physiological response [1,11]. Therefore, different thresholds for intervention are often recommended for different postnatal ages.

Cornblath et al. suggested 'operational thresholds' in 2000 and advised clinical intervention in 'symptomatic' babies for blood glucose concentration < 2.5 mM [11]. For babies with risk factors they suggested monitoring of blood glucose concentration, and close surveillance if <2.0 mM, with intervention if there is no increase post-feed, if abnormal clinical signs develop or if <1.4 mM. The same thresholds were advised for preterm and term infants. The authors acknowledge the empirical, expert-opinion basis of these thresholds, but justified them with a desire to provide operational thresholds high enough to provide a margin of safety and be applicable to a wide range of clinical aetiologies.

A review of the evidence was undertaken in a workshop for the National Institute for Child Health and Human Development in 2009 [10]. Recognising the lack of evidence, the workshop panel advised that repeated and prolonged very low plasma glucose concentrations should be investigated and treated, but did not specify blood or plasma glucose concentration thresholds or duration.

The American Academy of Pediatrics' current guide for management of newborns at risk born at ≥34 weeks' gestation includes an algorithm with suggested thresholds for intervention [3]. The advised thresholds depend upon postnatal age and range from 1.4 to 2.2 mM in the first four hours, 1.9 to 2.5 mM from four to 24 h and 2.5 mM for babies > 24 h old. In babies with clinical signs, the advised threshold

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