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Hypoglycaemic Thresholds: Screening verses Diagnosis? Physiological or Pathological?

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Identification and Management of Neonatal Hypoglycaemia in the Full Term Infant – A Framework for Practice

Thresholds for Hypoglycaemic Screening; a Cause for Concern?

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The new Framework for Practice highlights the limited evidence for our current clinical practice (1). It is helpful in emphasising the importance of accurate measurement of glucose concentrations, listening to the concerns of parents and acknowledging that untreated hypoglycaemia can have devastating longterm consequences. **However we have the following concerns**:

Screening thresholds

The Framework recommends lowering a commonly accepted screening threshold in infants considered to be at risk of hypoglycaemia to a level that at any other time of life would be considered harmful. It fails to acknowledge the differences between screening and diagnostic thresholds; something neonatologists are very familiar with in the management of babies with jaundice. Phototherapy is provided to many babies with bilirubin levels well below a harmful level to prevent a harmful level being reached. Screening interventions are intended to prevent harmful events. Such thresholds will inevitably mean many individuals are treated 'unnecessarily' to avoid the risk of significant harm. In 2000 Cornblath et al published guidance on 'operational thresholds' in keeping with the current BAPM framework (2). However, and possibly reflecting concerns about the lack of evidence for the safety of this lower operational threshold, in 2017 in the UK, >80% of neonatal units still used <2.6mmol/ as their defined hypoglycaemic threshold (3). A threshold of <2.6mmol/l provides an opportunity for intervention before damaging neuroglycopaenia occurs.

Alternative Fuels and Hyperinsulinism

What is an appropriate intervention depends on the whole clinical scenario, including the potential availability of alternative fuels. However, these are difficult to measure accurately at the cot side, and the clinical significance of particular levels in an individual in terms of physiology or pathology is still not entirely clear (4). Nevertheless, it is presumed that a hormonal milieu such as hyperinsulinism, that suppresses production of alternative fuels, is likely to increase risk of neurological damage.

In this respect we have concerns that the Framework provides incongruent advice in recommending an intervention threshold of <2.0mmol/L for infants of diabetic mothers and

growth restricted infants, but advises that blood glucose concentrations should be kept >3.0mmol/l in infants with suspected hyperinsulinism. Infants of diabetic mothers and growth restricted infants may also have transient hyperinsulinism (the diagnosis of which can be challenging and protracted in the newborn but is supported by raised cord c-peptide levels). Those with clinical experience of managing children with congenital hyperinsulinism, and the family support groups, are concerned that the new Framework is likely to result in delayed diagnosis and under-treatment of such infants, with potentially devastating consequences for the individual baby and family (5).

Evidence for harm

Most outcome studies are limited by the infrequent measurement of glucose concentrations after birth, as well as lack of specific tools used for neurological assessment. The latest follow up data from the CHYLD cohort, most of whom had continuous glucose monitoring in the first week after birth, showed that *neonatal glucose concentrations <2.6mmol/L were associated with substantially increased risk of impaired executive function and visual motor difficulty at 4.5 years, with greater risk in those with more severe (<2.0mmol/L), recurrent or clinically silent episodes.* (6) By the age of 4.5 years, children have increased capacity for complex problem solving and attention control; impairments that cannot be detected early in life. Previous studies have tended to focus on early and less specific deficits, and may not have been able to detect these specific problems.

All data in this field are currently limited by their observational nature, but executive function and visual motor skills, although not primary outcomes, were prospectively hypothesised to be affected by hypoglycaemia in the CHYLD Study. Furthermore, the apparent dose-response relationship between the severity and frequency of hypoglycaemic episodes and the risk of low executive and visual motor function increases the likelihood that this is a true association. The fact that the clinical teams were blinded to the continuously collected glucose data, and clinical decisions were made independently of these data, should also have reduced bias.

Nevertheless, this study was not restricted to babies born at term, and it is not possible in an observational study to exclude the possibility that unidentified antenatal factors may have contributed both to the hypoglycaemia and to the adverse outcomes. Despite this, the underlying mechanism for neurological injury may still be hypoglycaemia.

Finally, reducing screening thresholds, in the absence of sufficient reassuring outcome data, may result in discharge of babies who have not yet completed a successful metabolic transition after birth. This may result in more acute readmissions, as well as later neurodevelopmental impairment and so potentially more medico-legal claims for hypoglycaemic brain injury. This new framework will inevitably achieve its objective of reducing admissions of term babies, and will keep many mothers and babies together, but will there be a cost? (7)

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