Early Human Development xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

The potential risks and benefits of insulin treatment in hyperglycaemic preterm neonates

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ARTICLE INFO

Available online xxxx

Keywords:
Preterm
Hyperglycaemia
Insulin
Glucose
Amino acids
Parenteral nutrition

ABSTRACT

Preterm hyperglycaemia in the first 2 weeks of life is common under 29 weeks gestation and is associated with increased mortality and morbidity. While the definition of hyperglycaemia is reasonably consistent (>8 mmol/L) the treatment threshold varies widely in clinical practice. Insulin therapy is the most common approach despite international guidance urging caution because of hypoglycaemia. Significant hypoglycaemia is unusual outside studies targeting normoglycaemia. Insulin treatment also forms part of a nutritional strategy aiming to optimise early protein and energy intake so minimising the risk of preterm postnatal growth failure. Early parenteral amino acids also improve blood glucose control. There is some evidence of improved postnatal head growth with this approach but longer term neurodevelopmental studies are required. Glucose reduction is the alternative approach. This compromises early nutritional intake but avoids the potential for long-term cardiovascular and metabolic complications linked with high postnatal nutritional intakes and theoretically, insulin treatment.

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Hyperglycaemia in the first 2 weeks of life is well recognised in very preterm infants (VPI) less than 29 weeks gestation [1]. Acute concerns relate to the potential complications arising from osmotic diuresis [2] but more recent evidence has associated neonatal hyperglycaemia with greater mortality [3–5] and morbidity [3–5] including sepsis, retinopathy of prematurity, preterm brain injury, necrotising enterocolitis, and bronchopulmonary dysplasia. However, there is no definitive evidence of a causal relationship. It is possible that hyperglycaemia simply reflects immature postnatal adaptation and this, rather than hyperglycaemia, is the common mechanism. In addition, the degree of hyperglycaemia associated with increased morbidity is unclear. Hyperglycaemia is unusual in infants >30 weeks gestation without a recognised cause (eg sepsis, endocrine abnormality).

1. Mechanisms of preterm hyperglycaemia

The mechanism of hyperglycaemia in preterm infants is not fully understood but it may relate to both relative insulin resistance and defective islet β-cell function [6]. The former is suggested by:

1. Higher postnatal blood glucose and insulin levels compared to term equivalent [1]

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http://dx.doi.org/10.1016/j.earlhumdev.2015.08.011
0378-3782/

2. Failure to suppress glucose production despite hyperglycaemia (increased hepatic insulin resistance) [6]
3. Less abundant insulin-sensitive tissue (increased peripheral insulin resistance)
4. Hepatic and peripheral insulin resistance induced by raised inflammatory cytokines (eg sepsis, necrotising enterocolitis) that is more likely in the VPI [1].

Relative insulin deficiency (islet β-cell function) is suggested by the following [1,6–8]:

1. Preterm islet β-cells appear sensitive to glucose but secrete proinsulin and other precursors rather than insulin.
2. Preterm infants lack the postprandial incretin stimulation of insulin secretion.
3. Insulin deficiency may contribute to the early postnatal insulin-like growth factor I (IGF-I) deficiency in preterm infants.
4. The physiological early postnatal repopulation of islet β-cells is associated with reduced β-cell mass in preterm postnatal development.

Nutritional intake is also important, particularly with the recent focus on preventing early postnatal growth failure in VPI [9–11]. High glucose infusion rates are required to achieve target energy intakes at the upper end of the recommended range (hyperalimentation) and rates in excess of 6 mg/kg/min (8.7 g/kg/d) are more likely to be result in hyperglycaemia. The effect of amino acids (AA) on insulin secretion is well described in preterm infants [12,13] and provides a possible mechanism whereby early AA intake can improve blood glucose control. In animal studies, reduced β-cell mass is associated with early postnatal protein restriction [14]. Some AA may exhibit greater effects than others. Arginine is a particularly potent secretogue for insulin and there is evidence that poor preterm glucose control is associated with hypoargininaemia [15].

Early protein intake also affects insulin-like growth factor one (IGF-1) concentrations [16]. IGF-I lowers blood glucose levels by increasing peripheral glucose uptake and glycogen synthesis as well as suppressing hepatic glucose production. Neonatal IGF-I activity is directly altered by postnatal oral nutritional intake [16]. IGF-I levels fall sharply after preterm birth and take several weeks to recover [17]. There is evidence that IGF-I concentration are positively correlated with neonatal protein intake and nitrogen balance [16]. Thus, the interaction between nutrition and the somatotrophic axis is highly complex during the period early postnatal metabolic adaptation.

2. Definition and incidence of hyperglycaemia

There is a reasonably consistent definition of neonatal hyperglycaemia in the literature: 6.9–8.3 mmol/l [18]. In a study of infants <1500 g, 80% of infants had evidence of glucose levels >8 mmol/L in the first week of life [19]. However, the treatment threshold varies widely between neonatal services with nearly all UK tertiary neonatal intensive care units using blood glucose levels between 8 and 14 mmol/L (Fig. 1a) [20].The majority choose >12 mmol/l in 2 consecutive blood glucose measurements <4 h apart and choose insulin therapy as the intervention (Fig. 1b). A small number do not treat hyperglycaemia unless metabolic complications arise [21]. Similarly, an Australasian survey identified six different definitions of hyperglycaemia, with most units defining neonatal hyperglycaemia as a blood glucose level greater than 10 mM [22]. Despite having clearly defined treatment thresholds for blood glucose, hyperglycaemia policies rarely require assessment of actual glucose/carbohydrate intake. This is important because as described above, hyperglycaemia is more likely as the glucose infusion rate increases making differences in the incidence of treated hyperglycaemia particularly difficult to interpret. There is large variation between European NICUs in initial and target glucose intakes [23]. We have found that the majority of VPI become hyperglycaemic when infusion rates exceed 11 g/kg/d (7.6 mg/kg/min) [13]. Preterm

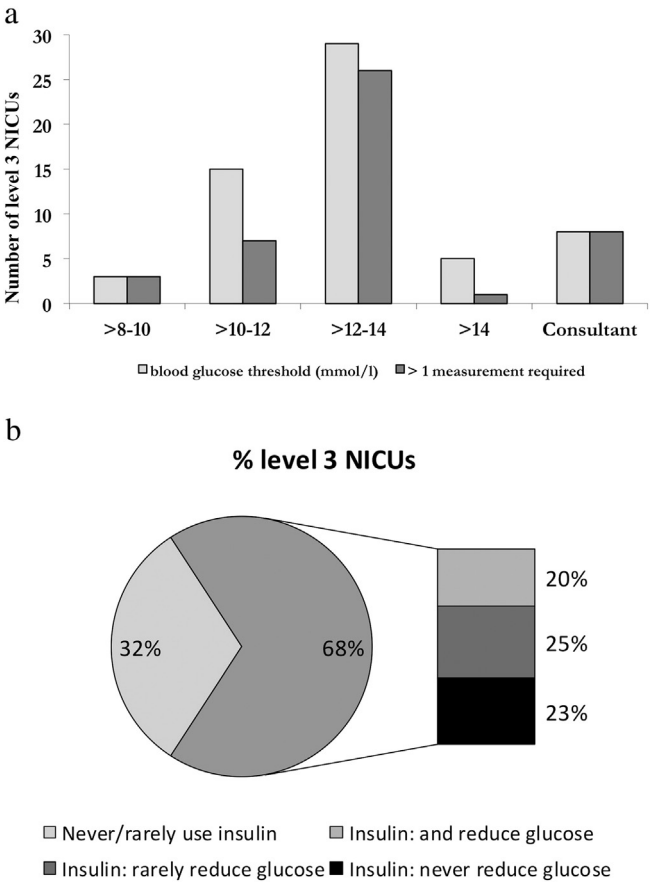

Fig. 1. a: Treatment thresholds for neonatal hyperglycaemia (blood glucose level, mmol/l) in UK level 3 Neonatal Intensive Care Units (NICUs). b: Teatment type for neonatal hyperglycaemia in UK level 3 Neonatal Intensive Care Units (UNICUs).

fluid intakes frequently require individual adaptation (impacting glucose intake) thus adding interpatient as well as inter-centre variability to interpretive problems. Calculating individual glucose intakes is therefore a key part of understanding and implementing hyperglycaemia treatment strategies.

The pattern of hyperglycaemia in VPI is described in Fig. 2a and b combining data from two recent randomised controlled trials [11,24]. Over the first 2 weeks of life, there is a rapid rise over the few days after birth and then a fall over the second week. Hyperglycaemia beyond day 14 is unusual. The pattern is independent of gestation (although the incidence is much more common at 23 weeks than 28 weeks gestation) and enteral feeding. This would be consistent with the early repopulation of beta cells described above or a postnatal increase in insulin sensitivity (or a combination of both). Fig. 2a and b shows the pattern of insulin use for a treatment threshold of 12 mmol/L. For a lower treatment threshold, the incidence increases and the peak for insulin therapy occurs earlier in the first week [25]. Fig. 2a and b reveals how increased carbohydrate (mainly glucose) and early AA intake (see below) modulate the incidence of hyperglycaemia without changing the underlying pattern.

3. Use of insulin in current clinical practice

A number of small observational studies have shown that insulin is an effect way to treat hyperglycaemia in the preterm infants. The American Academy of Paediatrics has supported the use of insulin for 30 years and many international nutrition surveys confirm widespread use of insulin [20–22]. UK surveys indicate one third of level 3 NICUs avoid insulin use (Fig. 1b), by limiting early glucose intakes and/or reducing glucose intake in the event of hyperglycaemia [20,21]. Glucose

Please cite this article as: Morgan C, The potential risks and benefits of insulin treatment in hyperglycaemic preterm neonates, Early Hum Dev (2015), http://dx.doi.org/10.1016/j.earlhumdev.2015.08.011