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Hyperglycaemia in preterm neonates: What to know, what to do

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ABSTRACT

Neonatal hyperglycaemia is a frequent complication in VLBW infants during the first week of life. The more common causes include high glucose intake, stress situations such as sepsis, NEC, and surgical treatments, as well as the administration of vasoactive drugs and methylxanthines. The appropriate definition is unclear. Hyperglycaemia has been associated with increased mortality and major morbidities. There have been insufficient randomized clinical trials to help in clarifying which infants should be treated, and there are insufficient data on the pharmacokinetics of insulin in these vulnerable patients.

1. Introduction

Neonatal hyperglycaemia is a common problem in VLBW premature infants receiving IV glucose infusions and it is probably secondary to an insufficient processing of pro-insulin by the immature pancreas and decreased insulin sensitivity of the liver. Therefore, the infant continues its glucose production despite hyperglycaemia [1].

Controversies arise when trying to define it, to determine its adequate management, and to evaluate its long and short-term implications. Latest studies performed in adults, infants and low birth weight (LBW) newborns have acknowledged its association with higher mortality and morbidity rates and a negative prognosis in the long-term [2,3]; which have led to a re-assessment of its correct diagnosis and workup.

Hyperglycaemia is quite frequent in the first week of life, an increased frequency being associated to a lower gestational age and birth weight as well as to severe clinical situations. It is still unknown which levels of plasma glucose could lead to damage. Significant osmolar changes could be related to IVH [4] in this group of patients. Some negative effects could have a direct relationship to osmolality [5], duration of episodes of hyperglycaemia and general clinical state of the infant.

2. Definition

Hyperglycaemia could be defined according to two different approaches: a) statistical and b) functional–clinical.

An arbitrary statistical definition of hyperglycaemia will take a value of 125–150 mg% (7–8.3 mmol/l) [6]. This definition comes from studies on term infants [7]. It should consider however, if the measure is in whole blood or plasma (15% higher).

A functional–clinical definition of hyperglycaemia will take it as a physiological response to keep cerebral metabolism in stress situations. In that case insulin could be used as treatment only in the presence of glycosuria with osmotic diuresis and dehydration [8]. There is an implicit weakness of this definition however since the glycosuria threshold varies according to each ELBW infant (a rare event with glucose <180 mg%) [9].

3. Aetiology

The most frequent cause of hyperglycaemia, particularly in ELBW infants, is the administration of IV glucose in excess of what that particular infant is able to handle. It is always important to rule out factitious hyperglycaemia occurring when blood was drawn from an IV line containing glucose as well as iatrogenic cases resulting from an inadvertent bolus from flushing an IV line.

VLBW infants frequently get hyperglycaemic when faced to stress generating situations such as sepsis, necrotizing enterocolitis, acute intracerebral bleeding, and also during or after surgery. In fact, sepsis and NEC are frequently suspected first when previously normoglycaemic infants develop hyperglycaemia in the absence of changes in the IV infusion rate or while being exclusively enterally fed. Interestingly hyperglycaemia is more frequent in fungal than in bacterial neonatal sepsis. Furthermore high blood sugar in candida septicaemia may appear 2 to 3 days before other clinical signs develop [10].

Hyperglycaemia may be also associated to medications, especially high-dose postnatal steroids, vasoactive drugs and theophylline [8].

4. Incidence

Literature reported incidences of hyperglycaemia vary between 20 and 80% due to lack of consensus related to its definition [11]. The most interesting information comes from a recently published sub-

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analysis of the control group (not receiving prophylactic insulin) from the NIRTURE study [12]: During the first week of life, hyperglycaemia (defined as glucose levels >145 mg% during more than 10% of the time) developed in 80% of 188 VLBW infants. Furthermore, 32% had glucose levels >180 mg%. It is important to mention that in this study blood glucose levels were continuously measured with a special device. Independent risk factors for hyperglycaemia were: lower birth weight and gestational age, sepsis, and the administration of inotropes and of lipid infusions. For the latter situations, the authors speculate that inotropes may reduce insulin secretion and increase insulin resistance and that lipid infusion could impair insulin sensitivity or increase availability of substrates for gluconeogenesis by the liver.

5. Pathophysiology

The intervening mechanisms for hyperglycaemia in ELBW infants are very complex, there being several inter-related factors such as: hepatic and pancreatic immaturity, insulin resistance, external glucose supply, increased catecholamines, stress, drug use (inotropic drugs, xanthine, corticosteriods), lack of enteral supply (leads to insulin secretion), etc.

Insulin increases the uptake and utilization of glucose, while inhibiting gluconeogenesis. "Insulin facilitates amino acid entry into muscle and protein synthesis, enhances fat synthesis in the liver and glucose uptake by adipose tissue and influences growth and lipogenic activity (as is exemplified by the appearance of babies born to mothers with poorly regulated diabetes at birth)" [8]. The preterm neonate responds to hyperglycaemia by secreting proinsulin peptides, which are identified as 'insulin' by standard assays but they are of variable biological potency [13]. The tissues of the preterm baby are more resistant to insulin as demonstrated by the fact that after birth, the preterm baby has higher plasma glucose and insulin levels than the term baby. Glucose production continues despite high glucose and insulin levels [7].

6. Low tolerance to glucose vs. hyperglycaemia: Who to treat?

To establish a safe operative level for hyperglycaemia, similar to the one proposed for hypoglycaemia, is a difficult task due to the fact that there are no scientifically supported reference values to date with which to approach this condition. Therefore, an operative-functional definition of hyperglycaemia based on all intervening potential factors leading to it could help define a safe approach to treatment and prevent any inappropriate therapeutic attitude that might result from taking an arbitrary glucose reference value with which to start treating the problem. This last behaviour could be even more dangerous than hyperglycaemia itself.

The need for glucose in a stable ELBW infant is established at approximately 6 mg/kg/min plus an additional 3 mg/kg/min for protein anabolism with a maximal oxidative capacity of 12 mg/kg/min [14].

The IV administration of 6 to 8 mg/kg/min may occasionally result in glycosuria but nobody has reported cases of osmotic diuresis and polyuria with these infusion rates. The blood glucose level at which an osmotic diuresis is triggered is unknown [8].

Blood glucose variability in VLBW infants receiving intravenous fluids is a very common problem. There is a relationship between the mean plasma glucose level in the hours before urine collection and the amount of glucose found in a urine sample. Although tubular reabsorption is quite efficient with normal or even moderately high blood sugar levels, it becomes incomplete at high filtered loads e.g. with blood glucose levels above 215 mg%. Even in such situations, the neonatal kidney will frequently concentrate the urine and osmotic dieresis is very infrequent. The current approach to the management of hyperglycaemia is quite varied: a) no treatment b) glucose restriction c) insulin infusion or a combination of b) and c) [7].

What could be the risk-benefit balance of treating hyperglycaemic episodes not leading to osmotic diuresis or increased osmolality?

Early insulin therapy has been proposed as prophylaxis or as a way to increase tolerance to glucose and therefore caloric intake in VLBW infants, especially in cases of mild hyperglycaemia. This technique seeks to facilitate increased glucose intake in parenteral nutrition. Several studies published between 1978 and 2003 tried to demonstrate its efficacy but the results were not convincing [15–19].

The Nirture [20] study published in 2008 randomized 389 VLBW infants receiving prophylactic insulin and additional glucose vs. standard care. There were no differences in the primary outcome (mortality at the expected date of delivery). While the group receiving insulin had a higher glucose intake and a better growth curve, it also had a higher incidence of hypoglycaemia and higher mortality at 28 days. The study had to be interrupted because of these unexpected risks.

The 2009 Cochrane revision [21] of randomized studies yielded no evidence that treating hyperglycaemia in VLBW infants could decrease mortality and morbidity rates. Therefore this revision could not ascertain that hyperglycaemia is the main reason for adverse outcomes or that it should be treated.

The physiologic response to stress results in hyperglycaemia, probably directed to assure metabolism and brain growth in situations where there is an increase in glucose consumption. To interrupt this response may not be beneficial.

A conservative approach would be appropriate for the management of ELBW infants with transient hyperglycaemia with values <200 mg% in the first days of life without massive glycosuria or polyuria; most cases would respond to a temporarily diminishing glucose flow between 4 and 6 mg/kg/min, administering adequate protein supply from birth and providing early minimal enteral nutrition.

A normal newborn has a maximal glucose oxidative capacity of around 12 mg/kg/min; higher infusion rates may result in conversion to fat [14]. We should also keep in mind that 8 to 9 mg/kg/min of glucose may be needed to support protein anabolism of ELBW infants. If hyperglycaemia and glycosuria persist with infusion at those rates, insulin treatment may be considered.

7. Neonatal diabetes

This is a very unusual condition. Some infants with intrauterine growth retardation develop severe hyperglycaemia requiring insulin treatment for several weeks. The condition improves but, in general, it relapses during adolescence or early adult life. Less frequently and probably in relationship with problems at a molecular level, some newborn infants develop permanent diabetes [22].

8. Complications of hyperglycaemia

Several studies have related hyperglycaemia to increased mortality, IV, ROP, increased oxidative stress, sepsis, NEC, longer hospital-stay and adverse long-term outcomes, etc. [2–4,23–27]. Most studies performed on preterm infants are retrospective. There are no data from evidence-based research concluding that hyperglycaemia in itself leads to damage or if it is simply a marker associated to severe pathology of the newborn which generates the damage. Neither is there certainty that keeping glucose below 250 mg/dl is better. Yet, what is known is that many infants who suffered severe hyperglycaemia can grow and develop without any problem.

There is a recent study from the Karolinska Institute on very low gestational age infants (<27 weeks) where hyperglycaemia (glucose >150 mg%) during the first 24 h. of life was an independent factor associated to increased mortality and reduction of cerebral white matter at a term detected by MRI [28]. Another recent study followed hyperglycaemic newborns to the age of 2 years. Hyperglycaemia was defined as at least 2 blood glucose levels of ≥10.0 mmol/L (180 mg/dL)

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during a 12-hour period. When comparing 33 patients with 66 controls, growth was similar but neurological and behavioural development was more frequently abnormal among those with neonatal hyperglycaemia [27].

9. Treatment

Insulin therapy may cause hypoglycaemia. The pharmacokinetics of insulin in ELBW infants is not well known. Information about its bio-availability and mean half life comes from extrapolations from studies on adults and paediatric patients. The references used to recommend treatment guidelines – like those by Neofax [29] – are not supported by pharmacodynamic studies performed on neonates [15,20,30–33]. Therefore it cannot be used as a reliable medication for this age group.

The Nirture study [20] observed increased mortality at 28 days in the group treated with early insulin as compared to the control group. This could point at insulin as an independent factor leading to bad neurological outcomes [27].

Neonatal hyperglycaemia management should start with a good etiologic diagnosis of intervening causes, taking into account that it is a physiological response to stress, e.g. sepsis and hypothermia.

It appears that current knowledge does not support the treatment of hyperglycaemia when it does not lead to a sustained increase in osmolality and/or dehydration by osmotic diuresis.

Some considerations should be taken into account when using insulin therapy.

Several authors have described insulin adsorption on the polyvinyl and polyethylene tubing [33–36] as a factor leading to diminished insulin availability for the patient. In VLBW infants with a continuum intake at low dose insulin infusion (concentration of 0.2 U/mL), revealed that blood glucose levels declined to,200 mg/dL (11.1 mmol/L) only after a median time of 19 h, with a range of 14 to 24 h [33] . Adding albumin improves insulin availability by reducing its adsorption to the tubes [37], but it results in higher costs and requires the administration of haemoderivates with their implicit risks [31].

Another alternative is to impregnate the tubing with an insulin solution at 5 IU per millilitre for 20 min before starting the infusion. This can significantly reduce insulin adsorption to the tubes thus permitting a 100% bioavailability at 8 h instead of the 24 h that may be required when the impregnation is not performed prior to infusion [33]. However, it is crucial to take into account this delay in obtaining the optimal response. To ignore it leads to increasing the insulin infusion rate before this period of 8 h, especially when an infant remains hyperglycaemic. This could generate the onset of hypoglycaemic episodes requiring a sudden decrease in the rate of infusion which in turn results in repeated major changes in plasma osmolality.

Insulin availability for preterm infants varies widely among the different units since the tubing used is of different material and length, and circuits are not changed at the same time schedule. According to the CDC, circuits should be changed every 96 h [38] . If we have a stable ELBW infant with an insulin infusion for a given flow, the circuit change will undoubtedly affect the received dose until the saturation of the new tubing is reached.

Certainly, more prospective studies are needed to determine the best way to prime the tubing, to change it, and to increase the infusion rate. For the time being, we recommend priming the tubing and not modifying the infusion rate for the first 8 h of infusion.

10. Conclusions

A higher than tolerated glucose intake is the most frequent cause of high blood sugar levels, which can improve when lowering the glucose load. In case of persistent hyperglycaemia, sepsis and other factors leading to neonatal stress should be ruled out.

Some neonatologists might be overestimating the dangers of hyperglycaemia. It should be remembered that levels of up to 150 mg% of blood glucose are very common in VLBW infants. Further, levels of 250 mg% frequently will not trigger diuresis. It seems more sensible to measure glycosuria rather than blood glucose when trying to determine the need for treatment. Prophylactic insulin treatment might bring more risks than benefits yet insulin could be used when glucose levels are over 215 mg%. Attention should be given to insulin adsorption to tubing since it can delay the onset of the optimal response. The great paediatrician, neonatologist and researcher Edmund Hey said: "Words act as shorthand for our thoughts: if we do not control them they start to control us. If we speak of a specific blood glucose level as being 'hyperglycaemic' when it is neither unusual nor hazardous, we soon start to act as though it is" [8].

11. Conflict of interest statement

The authors have no conflict of interest to declare.

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