S W I S S S O C I E T Y O F N E O N A T O L O G Y

G U I D E L I N E S

Prevention and treatment of hypoglycaemia in neonates with a gestational age from 35 0/7 weeks in maternity wards

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What's new

Changed operational threshold for neonatal hypoglycaemia to < 2.6 mmol/L (previously < 2.5 mmol/L)

Added oral dextrose gel 40% to prophylaxis and therapy of neonatal hypoglycaemia

Added new evidence on neurodevelopmental outcome after neonatal hypoglycaemia

Added new data on glucose profiles in well neonates over the first few days of life

Introduction

The aim of these recommendations is to give guidance in avoiding and treating hypoglycaemia in term and late preterm neonates from 35 0/7 weeks gestational age in delivery units and on maternity wards, i.e., level I units providing basic neonatal care according to the standards for levels of neonatal care in Switzerland. [1] This guideline does not cover management of preterm neonates < 35 weeks of gestation and sick term neonates who should be admitted to higher level units offering special, intermediate, or intensive care (levels of neonatal care IIa, IIb, and III in Switzerland).

Background

With the delivery of a newborn infant, several metabolic adaptive processes take place in order to ensure the shift from placental glucose provision and foetal glycogen synthesis to independent glucose production and regulation of the neonate. During delivery, endogenous glucagon and catecholamine levels rise 3 to 5-fold and initiate glycogenolysis, which in turn assures glucose homeostasis during the first few hours of life. Growth hormone and cortisol secretion during delivery promote gluconeogenesis, which becomes increasingly important after the first few hours of life. In parallel, insulin levels decrease. In order for glycogenolysis and gluconeogenesis to take place, involved enzymes and substrates such as glycogen, fat, and amino acids must be available. [2–5]

Even during optimal postnatal adaptation, blood sugar levels of term healthy neonates may be low during the first few hours of life. Thereafter, they rise slowly but steadily over the first day of life and remain stable to 48 h (mean (SD) glucose level, 3.3 (0.6) mmol/L) until a new plateau is reached by day four of life (mean (SD) glucose level, 4.6 (0.7) mmol/L). [6] Nevertheless, more than one third of term healthy neonates may have at least one episode of blood glucose levels below 2.6 mmol/L within the first days of life, particularly within the first 12 h of life. [6]

Glucose is the primary substrate for cerebral energy requirements. Neonates have high weight-adjusted glucose needs because of a relatively high weight of the brain in relation to total body weight. The brain can also use lactate or ketone bodies as an energy substrate, produced in case of lipolysis. [7] Thus the brain of a newborn infant is not completely dependent on glucose alone. For this reason, routine blood glucose monitoring is not warranted in term healthy neonates. By contrast, there are infants at an increased risk of neonatal hypoglycaemia, such as those being born after perinatal stress or to a diabetic mother, with relative hyperinsulinism as the main reason for transitional postnatal hypoglycaemia; [8] also, preterm and small for gestational age neonates are at risk as they have reduced glycogen pools and less fat storage, leading to a diminished capacity for lipolysis, which in turn results in insufficient delivery of ketone bodies to the brain. Furthermore, they show insufficient gluconeogenetic counter regulation in the presence of low blood glucose levels because of a lack of substrates for gluconeogenesis such as lactate, pyruvate, alanine and ketone bodies. Therefore, routine blood glucose monitoring is mandatory in these infants (see figure 1 for a list of infants at increased risk of hypoglycaemia). [3, 5, 9–15]

Early initiation of enteral feeds with breast milk promotes gluconeogenesis by providing the necessary substrates. Ketogenesis is enhanced due to fatty acids in the milk, and insulin secretion is only discretely increased in the presence of lactose in the milk. Administering glucose enterally on the other hand can lead to substantial insulin secretion and diminished glucagon production, thus delaying the necessary gluconeogenic and ketogenic homeostatic processes. For these theoretical reasons, feeding milk is far more advantageous than giving enteral glucose. [3, 9, 10, 14]

Despite decades of research, there is still no consensus definition of hypoglycaemia in neonates. There are four concepts for defining glucose thresholds, based on the following factors: i) Clinical symptoms (so-called symptomatic hypoglycaemia); ii) Epidemiological data; iii) Acute metabolic, endocrine and neurological findings; iv) Long term neurological outcome. None of those concepts are satisfactory and each one has disadvantages, some of which are significant. [2, 3, 10, 12, 15–20] Thus, the SSN refrains from providing a specific definition and prefers to define operational thresholds for prevention and treatment of hypoglycaemia in neonates.

The effect of postnatal hypoglycaemia on neurodevelopmental outcome is still unclear. Recent data suggest possible late effects: In a prospective cohort study of 528 newborns with a gestational age ≥ 35 weeks, primarily recruited on the basis of maternal diabetes, the authors found no difference in neurodevelopmental outcomes at 2 years of follow-up in children after postnatal hypoglycaemia (<2.6 mmol/L) vs. children without hypoglycaemia. [21] However, follow-up of the same cohort at the age of 4.5 years revealed reduced visual motor and executive functions in children exposed to postnatal hypoglycaemia, with the highest risk in those who had experienced severe (<2.0 mmol/L), recurrent, or clinically undetected hypoglycaemia. [22] Further, a recent population-based study compared neurodevelopmental outcome at the age of 2 to 6 years in 1'500 neonates from 34 weeks of gestation with moderate (<2.2 mmol/L) hypoglycaemia vs. 99'560 neonates without postnatal hypoglycaemia. In this cohort, the adjusted risk for any developmental delay, motor developmental delay and cognitive developmental delay was increased for all three parameters. [23] Lastly, the most recent randomized trial comparing 2.0 mmol/L *versus* 2.6 mmol/L as a treatment threshold of asymptomatic hypoglycaemia in healthy neonates from 35 weeks of gestation found no difference in psychomotor development at 18 months of age. [24] However, long-term outcome data from this study are not yet available. Given the above evidence that neurodevelopmental issues after neonatal hypoglycaemia may

be underreported prior to preschool age, we currently recommend not to adopt a 2.0 mmol/L threshold.

Differential diagnosis

Hypoglycaemia in neonates is a diagnostic finding that may originate from a multitude of underlying causes. It may occur as an expression of perturbed postnatal metabolic adaptive processes or as a non-specific symptom of various diseases (i.e. infection, asphyxia, polycythaemia). Hypoglycaemia is very common in preterm and/or small for gestational age infants (see guideline 'Care of infants with a gestational age between 34 and 37 weeks'). [25] In most cases, the history and clinical exam will help to elucidate the main reason for hypoglycaemia (e.g., prematurity, intrauterine growth restriction, maternal diabetes). [26] In case of persistent or recurrent hypoglycaemia despite adequate oral supply of milk and dextrose gel, neonates should be immediately transferred to a level II or level III unit for intravenous glucose treatment and diagnostics to rule out persistent hyperinsulinism, metabolic disorders, or endocrinopathy. [27]

Diagnostic considerations

Requirements for devices measuring neonatal blood glucose levels are high: Test results must be readily available and be precise in the low range, analysis should require a minimal amount of blood, and the method should be cost-effective. The gold standard is enzymatic laboratory determination via the hexokinase method. However, a delay in sample processing may result in a reduction of glucose levels due to red cell glycolysis (0.3 mmol/L/hour). [28] For practical reasons, bedside methods using portable devices are commonly used. The accuracy of different bedside devices vs. the hexokinase method to determine hypoglycaemia has been examined in numerous studies. [29–35] In summary, most devices overestimate blood glucose levels. Depending on the device used, deviations can be between 0.2 and 0.6 mmol/L when blood glucose levels are in the range of 2.0 to 2.5 mmol/L. On the other hand, occasionally, blood glucose values measured by a bedside method may be falsely low. Since bedside measurement of neonatal blood glucose levels is standard of care in maternity wards, measurement error must be taken into consideration. Regular calibration and quality control of these devices is mandatory. Upon introducing any new device into clinical practice, prior calibration against the hexokinase method in neonates is warranted. [36]

Assessment of hypoglycaemia

Ideally, hypoglycaemia should be defined individually, depending on clinical context. However, feasibility and safety of such an approach seems questionable at best. For pragmatic reasons, a pre-determined operational threshold (independent of the method/device) is used in clinical practice. Recent data suggest that the factor being most predictive of neurodevelopmental outcome in the first 48 hours after birth is glucose instability, i.e., the proportion of measurements or duration of time outside a central range of 3 to 4 mmol/L while hypoglycaemia per se, defined as a blood glucose concentration < 2.6 mmol/L measured by the hexokinase method, was not associated with an adverse neurologic outcome at 2 years of age when prompt treatment was provided at this threshold. [21] Since many hospitals use portable bedside devices, some of which potentially overestimate blood glucose, the operational threshold to consider neonatal hypoglycaemia in this SSN guideline is set as follows:

> A blood glucose level < 2.6 mmol/L in infants ≥ 35 0/7 weeks gestation determined by any device indicates hypoglycaemia and requires intervention

Algorithm for management of neonates *at an increased risk of* hypoglycaemia

Figure 1 shows recommended preventive measures (early feeds, dextrose gel, additional feeds), blood glucose tests, and therapeutic measures in neonates who are at an increased risk of hypoglycaemia. Additionally, glucose consumption should be minimized by keeping body temperature within normal range (see guideline: Care of infants with a gestational age between 34 and 37 weeks). [25]

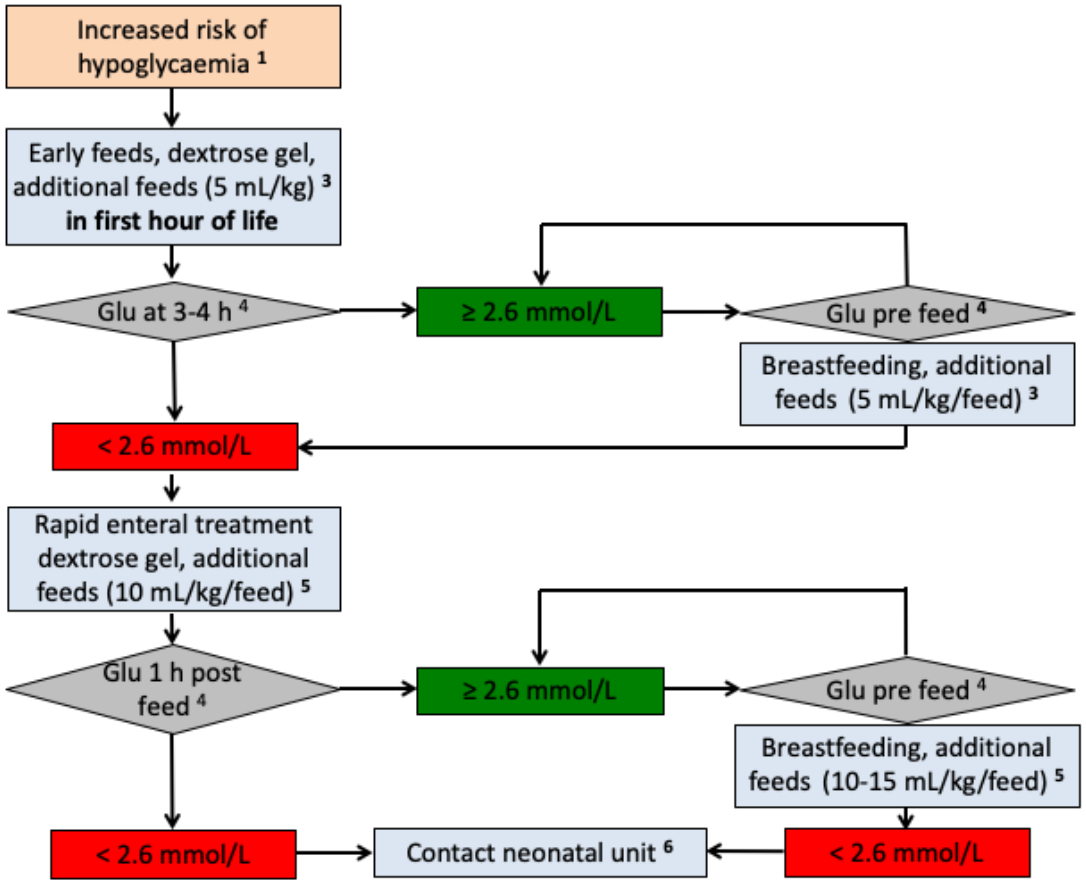

Figure 1: See pages 6 and 7 for explanation of footnotes; (Glu = blood glucose levels).

Algorithm for monitoring and treatment of neonates *with suspected* hypoglycaemia

Figure 2 shows blood glucose tests and therapeutic measures in neonates with symptoms suggestive of hypoglycaemia.

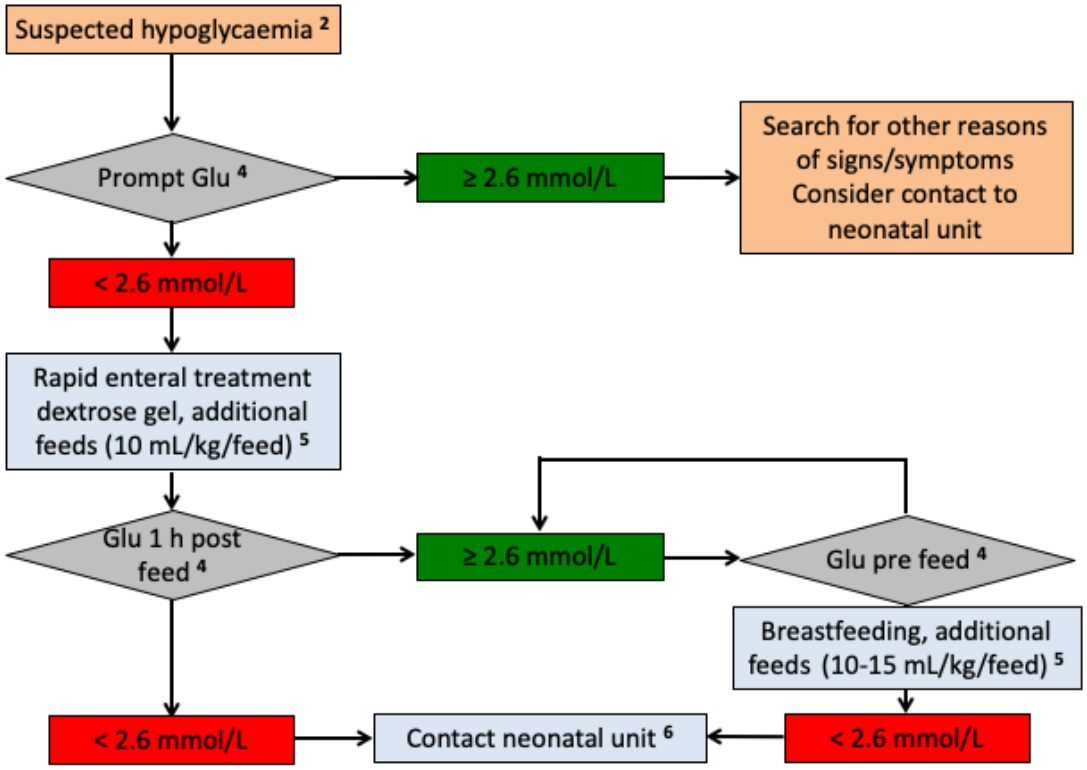

Figure 2: See pages 6 and 7 for explanation of footnotes; (Glu = blood glucose levels).

The following situations must be avoided or, if they occur, be rapidly and resolutely addressed as they are associated with an increased risk of neurological impairment. [22] Contact with a neonatal unit should be sought immediately and the necessary steps in treatment introduced without delay in the following cases:

- severe hypoglycaemia < 2.0 mmol/L
- prolonged hypoglycaemia > 4 hours
- recurrent hypoglycaemia

Explanation of footnotes in algorithms

1. Increased risk of hypoglycaemia

- Preterm infants < 37 0/7 weeks gestation
- Maternal diabetes (including both women treated only with dietary intervention and those receiving insulin)
- Birth weight < 2500 g at term or birth weight < 3rd percentile
- Birth weight > 4500 g at term or birth weight > 97th percentile
- Sick newborn infants (e.g., asphyxia, sepsis, respiratory distress, haemolysis)
- Hypothermia (< 36.5° C)

2. Suspected hypoglycaemia

Symptoms suggestive of hypoglycaemia include neurological (muscular hypotonia, hyperexcitability, apathy, seizures), circulatory and respiratory (apnoea, cyanosis, pallor, tachycardia, bradycardia), and other symptoms (tremors, jitteriness, sweating, hypothermia). If hypoglycaemia leads to neurological symptoms, one assumes that the brain is not receiving sufficient glucose and that sufficient alternate energy sources are not available. For this reason, rapid and effective treatment must be initiated. Symptoms of hypoglycaemia are non-specific. Therefore, other diagnoses should be considered if symptoms persist despite adequate treatment.

3. Early and additional feeds, dextrose gel

Antenatal expression of breast milk (mother's own milk)

Some hospitals encourage antenatal expression of mother's own milk, assuming that feeding expressed mother's own milk to babies at risk of hypoglycaemia may help to improve blood glucose concentrations after birth or treat hypoglycaemia. Existing data suggest that expressed mother's own milk is almost always of very small volume and has no meaningful effect on blood glucose concentrations. [37] On the other hand, there is no evidence of harm and prenatal expression may reduce the use of formula milk. [38]

Early breastfeeding

Newborn infants at increased risk of hypoglycaemia should be offered skin-to-skin contact and early breastfeeds. This should be started immediately after birth, within 1 hour after birth at the latest. During the first 2 to 3 days of life, the infant should be breastfed every 2 to 3 hours.

Prophylactic dextrose gel

A single dose of 200 mg/kg dextrose 40% gel (0.5 mL/kg), given at 1h after birth and massaged into the buccal mucosa, reduces the risk of neonatal hypoglycaemia. This is a general approach for infants at risk and not limited to infants from diabetic mothers. [39]

Formula milk

Immediately after breastfeeds, the infant may be offered supplemental formula milk (5 mL/kg body weight) until sufficient amounts of mother's own milk are available.

4. Blood glucose tests

Blood glucose levels may be determined by bedside tests. In asymptomatic newborn infants at an increased risk of hypoglycaemia, the first blood glucose level should be determined at the age of 3-4 hours of life, i.e., just before the second feed. In case of a documented hypoglycaemia, the blood glucose level should be determined again within 1 hour as to assess the treatment effect. If the blood glucose level is ≥ 2.6 mmol/L, further blood glucose tests are indicated before the next feeds. If three consecutive levels are normal, further blood tests may be discontinued. In case of symptoms suggestive of hypoglycaemia, the blood glucose level must immediately be determined.

5. Enteral treatment

Diagnosis of hypoglycaemia requires therapeutic consequences without delay. A single dose of 0.5 mL/kg (200 mg/kg) dextrose 40% gel should be massaged into the buccal mucosa immediately prior to a breastfeed as it reduces the risk of treatment failure and admission to the neonatal unit, improves breastfeeding compared to placebo, does not negatively impact neurodevelopment, and is inexpensive. [40, 41] Repeat doses of dextrose gel within the first 48 h of life may be considered, however, in cases of recurrent hypoglycaemia, a neonatologist or paediatrician should always be consulted. Concomitant treatment consists of offering breast milk or formula milk (10 mL/kg body weight). Over the first 2 to 3 days of life, additional feeds on top of breastfeeds should be offered 2-3 hourly, for a total of 10-15 mL/kg/feed. In general, oral glucose solutions (e.g., glucose 10% orally) are not recommended. In case of feeding difficulties, competent care givers may give milk via a feeding tube. Here, seeking advice from a neonatologist or paediatrician is recommended.

6. Contacting the neonatal unit

If hypoglycaemia cannot be corrected with enteral feeds and dextrose gel, intravenous glucose should be administered. This treatment usually is accomplished in a neonatal unit (levels of neonatal care IIa, IIb, and III in Switzerland). [1] In case of severe, prolonged, or recurrent hypoglycaemia, do contact the closest neonatal unit to discuss further measures.

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