A Concept Map of Neonatal Hypoglycemia

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Abstract

Objectives: To analyze current management of neonatal hypoglycemia and establish a concept map based on testimonies from physicians who use capillary blood glucose tests to guide management.

Methods: This was an observational, descriptive, mixed qualitative and quantitative study. A questionnaire was administered to physicians, seeking to characterize their responses to neonatal hypoglycemia in pregnancy, labor and delivery, and the immediate neonatal period. Data collection was performed with two groups of Brazilian physicians: neonatologists (group GN) and pediatricians (group GP). A Likert-scale was used to collect responses. The Mann-Whitney test and Fisher’s exact test were used for statistical analysis of continuous and categorical variables respectively. Statistical significance was accepted at 5%. Principal components analysis with varimax rotation and Kaiser normalization was used to verify the structure of question/answer factors in the two groups of professionals. A concept map was constructed using the Cmap Tools Knowledge Kit, version 5.05.01.

Results: Of the 98 questionnaires analyzed, 34.7% were completed by neonatologists (n=34/98) and 65.3% by pediatricians (n=64/98). Mean age in the two groups (GN and GP) was 42.4 years (SD: 11.78; 95% CI: 40.10, 44.88; p=0.597), with a significant difference in age in men (mean=50 years; SD: 10.35; 95% CI: 45.20, 54.90; p<0.001); 79.2% of respondents (n=78/98) were women. Overall, 32.7% of respondents (n=32/98) claimed they did not currently work with neonates. Respondents in GN had completed more postgraduate courses (p=0.38). The two groups responded similarly to all questions. The responses highlighted the importance of values lower than 40 mg/dL in the diagnosis of neonatal hypoglycemia, as well as the indication of intravenous infusion when glucose was below 40 mg/dL in symptomatic neonates. Immediate institution of periodic capillary blood glucose measurement was recommended for the following groups of neonates: those born to diabetic mothers, those with intrauterine growth restriction, small for gestational age, large for gestational age, preterm neonates, septic neonates, and those with birth asphyxia.

Conclusions: Capillary blood glucose is part of routine neonatal management, especially preventive, in light of the possibility of neonatal hypoglycemia. Our findings highlight that, in high-risk gestational groups, the entire neonatal team should be focused on the risk of hypoglycemia. The development of management algorithms based on the use of peripheral blood glucose test strips has contributed to streamlining the management of neonatal hypoglycemia.

Keywords: Hypoglycemia; Newborn; Maps; Practice guideline; Principal components analysis

Introduction

Hypoglycemia is a matter of heated debate in neonatology, particularly regarding its clinical definition and the optimal timing for intervention [1]. It is noteworthy that high levels of blood glucose can also cause damage during infant development, depending on the preference for glycolysis, oxidative and/or ketone metabolism, time, energy demand, deposition, etc. as discussed by Adamkin [2,3]. The current evidence base for glucose screening and treatment of asymptomatic infants includes reducing the risk of achieving higher-than-desirable glucose levels, which may be associated with glucose instability and, perhaps, adverse neurological outcomes with nonketotic hyperglycemia.

It is known that some neonates are more likely to develop hypoglycemia than others [4], and that low blood glucose levels can lead to permanent central nervous system damage [5]. The cut off level which should prompt treatment remains unclear, especially in asymptomatic neonates [6].

Cut off points for diagnostic and management considerations have been discussed since the 1930s [7], including in preterm neonates [8], the most important factor to bear in mind is that glucose meters overestimate the actual plasma level of glucose [9]. Glucose levels in arterial blood are 10-15% higher than in venous blood, and levels in plasma are 10-15% higher than in whole blood [10].

In low-complexity neonatal units, screening for hypoglycemia is done using test strips, which allow rapid bedside quantification of glucose levels. The specimens collected for test-strip reading in standard glucose meters are usually obtained from capillary blood. Any capillary glucose level <40 mg/dL should prompt confirmation of actual plasma glucose levels as soon as possible. A recent study measured capillary blood glucose levels using three different glucose meters and compared these measurements to levels quantitated by the hexokinase method. The authors concluded that none of the devices yielded satisfactory results. However, they noted that the overestimation of glucose levels by these devices could enable early detection of hypoglycaemia [9].

Obtaining immediate accurate measurements of actual blood glucose has long been difficult or even impossible in low-complexity settings, considering that symptomatic hypoglycemia – especially in high-risk groups – must be addressed quickly, and that the decision to infuse glucose intravenously (or not) must be made immediately.

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Starting from the premise that all newborns are vulnerable to declines in blood glucose levels, we presumed that physicians acting in the perinatal setting would be able to contribute with descriptions of their practical attitudes toward suspected cases of neonatal hypoglycemia, and that these descriptions could be used to develop a flowchart for management of this condition based on samples obtained from rapid capillary blood glucose testing.

Within this context, the present study sought to construct a concept map of neonatal hypoglycemia based on the testimonials of specialist physicians whose management of this condition is based on point-of-care capillary blood glucose testing.

Subjects and Methods

This was a mixed qualitative/quantitative, descriptive, observational study. A semi-structured questionnaire was administered to specialized physicians in order to collect information on their attitudes toward management of neonatal hypoglycemia.

The sample included two groups

Generalist pediatricians and specialist neonatologists, all agreed to take part in the study, in accordance with Brazilian National Health Council Resolution No. 466/12.

The questionnaire was divided into two parts. The first part was designed to collect general data, including age, sex, month and year of medical school graduation, and whether the respondent had pursued postgraduate studies in Neonatology after completing training in Pediatrics.

The second part of the questionnaire was subdivided into two stages

Eight multiple-choice questions with three to five possible answers each, followed by two open-ended questions. One open-ended question inquired as to management practices for asymptomatic neonatal hypoglycemia, regardless of cause; the second such question asked the respondent to identify any variable they regarded as important when deciding how to manage neonatal hypoglycemia which had not been addressed in the questionnaire.

The questionnaire then collected information on several factors related to neonatal hypoglycemia, including maternal problems related to hypoglycemia (Diabetes, Hypertensive disease, Systemic disease, Breastfeeding), delivery (Route of delivery: Vaginal, Surgical), neonatal factors (Gestational age/Birth weight: SGA, AGA, LGA; Neonatal conditions: sepsis, asphyxia, IUGR, congenital infections), and analytic factors (Capillary glucose level deemed diagnostic of neonatal hypoglycemia; Level deemed to prompt oral supplementation of breastfeeding; Level deemed to prompt intravenous glucose infusion). Responses were scored on a Likert-type scale (Completely disagree (1); Disagree (2); Neither agree nor disagree (3); Agree (4); Completely agree (5); or Never (1); Occasionally (2); Sometimes (3); Often (4); Always (5)).

During the study (2013), questionnaires were delivered personally by one of the investigators to Pediatrics and Neonatology departments in the state of Rio de Janeiro, Brazil. Prospective respondents were asked to reply by e-mail. They received an example questionnaire demonstrating how the research instrument should be completed. Throughout the data collection period, the investigator was available to clarify any doubts regarding proper completion of the instrument.

Initially, each respondent was identified only by level of proficiency in neonatal care, divided into two groups: non-neonatologist pediatricians (GP) and neonatologists (GN). The latter group comprised pediatricians who had completed a residency program in Neonatology, and/or had at least 5 years’ experience working in a specialized neonatal unit, and/or were board-certified as neonatologists by the Brazilian Society of Pediatrics.

The demographic variables collected were gender (male or female), time since graduation (<10 years or >10 years), postgraduate medical studies (residency/specialist training), setting of postgraduate studies (university hospital or otherwise), and whether the respondent currently works at a service that provides Neonatology training (yes or no).

The eight statements concerning neonatal hypoglycemia were scored from 1 to 5 on the aforementioned Likert-type scale of agreement. The wording of questionnaire items was guided by keywords selected on the basis of the recent literature on the topic. Multiple-choice questions were also based on the literature [10-26].

To construct the concept map, a graphic-based tool was used to organize and represent content. Concepts were represented by circles or boxes, and relationships between them were denoted by lines. Respondents’ answers to the research instrument were the basic substrate for plotting the concept flow.

Our analysis strategy consisted of first calculating Cronbach’s alpha coefficients, which define the reliability of different respondents’ answers on the same measurement scale by displaying the mean correlation between questionnaire items. Cronbach’s alpha values range from 0 to 1, and are deemed to represent consistency that is very good (>0.9), good (0.8-0.9), fair (0.7-0.8), poor (0.6-0.7), or unacceptable (<0.6).

The Keiser-Meyer-Olkin (KMO) test measure of sampling adequacy shows the strength of connection between variables. High values (0.5-1.0) are indicative of appropriateness of analysis. Values below 0.5 suggest the factor analysis may be inadequate.

Bartlett’s test of sphericity tests the null hypothesis that the correlation matrix is an identity matrix (variables are not correlated; correlation coefficients would be zero). In this case, principal component analysis cannot be performed. We want this test to be significant and have a value less than 0.05. Principal components analysis was used to evaluate the association between the constructed model and the degree of agreement between respondents. The core purpose of this analysis was to establish, in a homogeneous group with a strong correlation between variables, a coefficient without the initially existing correlation. The first component corresponds to the axis with the greatest variability, and the second component, to the axis with the second greatest variability. These exploratory models are based on the total variance of responses, and the two first components explain the largest percentage of response variability. Eigenvectors are a set of axes (components) extracted from a similarity matrix. Eigenvectors correspond to the length of the eigenvectors, and, thus, to their importance in explaining total variance in the data. Orthogonal Varimax Rotation maximizes the loading of each variable onto the new components and minimizes the number of variables that have high loadings on each component.

Principal component analysis was used to evaluate the association between the constructed model and the degree of agreement between respondents. The concept maps themselves were built in Cmap Tools.
The Kaiser-Meyer-Olkin measure of sampling adequacy and Bartlett test (GN=0.586/p=0.000; GP=0.586/p=0.000) supported the use of principal components analysis on this database. All measurements clearly showed that the two first components explained 65.52% to 100.00% of absolute variance in GN and 65.52% to 100.00% in GP, respectively.

In both groups, the contribution of each component showed consistency between the loaded values and the absolute frequencies of each item answered, both for the first (1C) and for the second (2C) component. Unfilled fields corresponded to factor loadings <0.66. There was also an evident lack of correspondence of loadings in GN, both regarding maternal diabetes – which respondents unanimously (34/34) agreed should prompt blood glucose controls – and regarding cutoff blood glucose values that should prompt oral feeding and IV dextrose. High factor loadings (>0.66) and a slightly higher variability of responses in GN might explain these higher loads of responses regarding blood glucose values >50 mg/dL.

In the subjective portion of the instrument, with open-ended questions, when respondents were asked to describe their immediate management of asymptomatic neonatal hypoglycemia, as determined by a low capillary blood glucose measurement during rooming-in, regardless of cause, GP responses agreed with GN responses regarding encouragement of breastfeeding and/or complementary oral formula/pasteurized pumped breast milk, in addition to measuring blood glucose again after management.

When asked whether any variables other than those covered in the research instrument were important when deciding how to manage neonatal hypoglycemia, and, if so, to describe these variables in their own words, just over 26% of GN respondents and more than 53% of GP respondents replied that no additional variables were needed other than those already covered in the questionnaire. Among those who replied, many considered that other variables were relevant, most noted that consideration of the clinical picture/symptoms and of the possible causes of neonatal hypoglycemia were important variables when deciding how to manage such episodes.

The concept map constructed from the responses of physicians involved in neonatal care is shown in Figure 1.

This map was constructed using pooled data from both groups, as their responses were highly similar.
TABLE 1: Agreement, Cronbach’s alpha coefficients, and two principal components solution with KMO/Bartlett statistics in the neonatologist (GN) and pediatrician (GP) groups.

Proper assistance at the time of delivery is essential, as low vitality (perinatal asphyxia) is associated with hypoglycemia. The pathological changes caused by neonatal asphyxia can often cause derangements in glucose metabolism. Anaerobic glycolysis supervenes, with a decline in energy production and increased glucose consumption. These neonates often feed less and consequently absorb less nutrients, becoming more susceptible to hypoglycemia after rapid depletion of glycogen stores [27,28].

Magnetic resonance imaging (MRI) suggests that the occipital lobe may be particularly vulnerable to insults caused by hypoglycemia. Other cerebral complications involve global visual perception (areas within the dorsal visual cortex) and problems of executive function (skills essential for learning, interaction with the environment, working memory, reasoning, task switching, and problem-solving). At age 2 years, these neonates exhibit higher rates of sensorineural involvement, processing difficulties, and multiple secondary problems related to growth and development. Therefore, providers involved in neonatal care must be ever vigilant to any potential inability of newborns to consistently maintain preprandial glucose concentrations >50 mg/dL up to 48 h of age and >60 mg/dL after 48 h of age [1].

Discussion

Assessment of the clinical practices of physicians who provide perinatal care revealed that both those trained as generalist pediatricians and those trained as specialist neonatologists respond similarly to neonatal hypoglycemia.
Among maternal problems occurring in the prenatal period that should prompt periodic blood glucose controls in the neonate, diabetes was cited most often by respondents in both groups. Some studies have reported improvements in the management of diabetes with more appropriate drug combinations, new proposed therapeutic approaches [12] and even development of screening methods for gestational diabetes [13]. These advances are necessary, as glucose imbalances during pregnancy can cause irreversible damage to the fetus and newborn. Neonatal hypoglycemia remains a leading cause of morbidity [14]. Although neither group demonstrated a direct concern with hypertensive disease of pregnancy, studies have raised concerns regarding increasing body mass index in pregnant women [15], and it is becoming increasingly clear that obesity and diabetes go hand in hand [16]. It is also important to address the relationship between pregnancy-induced hypertension and disorders of fetal development, from intrauterine growth restriction (IUGR) [17,18] to neonates large for gestational age (LGA) [19] and even preterm birth [20,21] all of which facilitate the development of hypoglycemia. In their answers to the open-ended questionnaire items, the respondents also noted maternal medication use as an important factor, as many drugs (beta blockers, chlorpropamide, tocolytics, benzthiazide) can suppress the catecholamine response and prevent glycogenolysis, or stimulate the pancreatic beta cells. An even greater concern is the growing use of antidepressants during pregnancy, which may be facilitating the development of neonatal hypoglycaemia [22]. After birth, breastfeeding-related problems must be prevented, as they can be a cause of metabolic disorders, including derangements in blood glucose. This could be prevented by strict hypoglycemia prevention protocols [23] or by existing, well-established programs (kangaroo mother care) [24].

The mode of delivery had no influence on the decision to screen for hypoglycemia. Conversely, most respondents in both groups would never request blood glucose controls on the basis of this factor alone.

There was no surprise regarding management of SGA [16] and LGA [17] neonates: respondents’ practices confirmed that inadequacy for gestational age raises concerns with regard to hypoglycemia. Likewise, preterm birth (<37 weeks GA) was concerning to all respondents as a driving factor of hypoglycemia. Responses showed that, in clinical practice, there is a trend to prescribe blood glucose controls when neonates are born premature. GP respondents were more concerned with the need to control blood glucose in preterm infants born at <34 weeks, whereas in GN respondents, the preferred cut off point was 37 weeks.

In both groups, when inquired as to the role of continuous blood glucose control in the presence of neonatal morbidity, sepsis was the situation most likely to prompt glucose measurement orders, despite wide variance in responses. This was to be expected, as sepsis and asphyxia are the leading causes of interfacility transfer of neonates [25]. Secondary but still great importance was assigned to asphyxia and intrauterine growth restriction, while in utero infections were mentioned but less likely to prompt concern. It bears stressing that perinatal asphyxia, especially in neonates with intrauterine growth restriction, leads to poor metabolic adaptation in the first hour after birth [26].

Most physicians in both groups defined hypoglycemia as a blood glucose level <40 mg/dL, although they highlighted the importance of assessing the clinical picture/symptoms as well as blood glucose measurements alone to ensure more effective measurement. There is an increasing concern with optimal cutoff values for diagnosis of hypoglycemia and initiation of therapy, as the plasma glucose concentration associated with neurological damage is still unknown [25], although said damage is known to be permanent [5]. Thus, the current trend would be to consider a diagnosis of hypoglycemia at relatively higher glucose levels (<2.6 mmol/L or 47 mg/dL) [27]. So as to select a wider population for intervention and decrease the likelihood of failing to treat neonates who may develop future morbidity as a result of undiagnosed hypoglycemia. Within this context, it bears stressing that point-of-care test strips are known to overestimate serum glucose levels [9], which should be taken into account when addressing potential cases of hypoglycemia. Respondents revealed...
that, in clinical practice, they tend to prescribe complementary oral feeding when blood glucose is 20-50 mg/dL in asymptomatic infants, while prescribing IV dextrose in cases of blood glucose <20 mg/dL, regardless of the presence of symptoms, or <40 mg/dL in the presence of symptoms. It should be noted that the proportions of responses in the GN group were in agreement as to this concept of prescribing oral feeds vs. IV dextrose.

Several problems were encountered when conducting this study. These included resistance to diagnosing hypoglycemia on the basis of capillary blood screening alone, considering that most clinical algorithms mandate peripheral rather than capillary blood collection. Traditionally, glucose measurements in peripheral blood are considered the standard to define bedside management. However, it is known measurements in plasma from freshly centrifuged blood obtained from a central venous catheter would be the gold standard for accurate confirmation of low glucose levels. Other challenges included the low response rate, which led to a sample size insufficient for generalization of our findings. We believe that, in view of the small sample size, some statistical tests may have behaved unexpectedly. The most rewarding part of this study was the construction of a concept map based on the opinions of experienced providers, which demonstrated the simple response required in an often harrowing clinical event (neonatal hypoglycemia).

In conclusion, our findings highlight the fact that, in high gestational risk groups, the entire neonatal care team should be focused on the risk of hypoglycemia. The use of certain specific drugs during pregnancy should raise red flags of this risk. The development of an algorithm for neonatal hypoglycemia management based on peripheral blood samples and bedside screening using test strips and glucose meters could contribute to streamlining management of neonatal blood glucose levels. Based on the experience of our respondents, we were able to conclude that intravenous glucose infusion is always indicated in cases of capillary blood glucose <20 mg/dL, regardless of the presence of symptoms, or <40 mg/dL if symptomatic.

What is already known on this topic:

• Hypoglycemia in newborns causes permanent damage to the central nervous system.

• Problems related to pregnancy, birth conditions, and neonatal and postnatal morbidity are all implicated in the development of neonatal hypoglycemia.

Although there is no consensus about the optimal serum glucose cutoff levels which define hypoglycemia, procedures to address low blood glucose in newborns (glucose gel) have been implemented at several maternity facilities.

What this study adds:

• The presence of glucose disorders, feeding/dietary disorders, and/or the use of specific drugs during pregnancy should alert the perinatal care team to the risk of neonatal hypoglycemia.

• The development of neonatal hypoglycemia management algorithms based on the use of peripheral blood glucose test strips can contribute to streamlining the management of neonatal blood glucose levels.

• In our respondents' experience, intravenous glucose infusion is indicated whenever blood glucose is <20 mg/dL, regardless of the presence of symptoms, or <40 mg/dL when symptoms are present.

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