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SYMPOSIUM

Hypoglycemia in Critically Ill Children

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Abstract

Background:

The practice of glycemic control with intravenous insulin in critically ill patients has brought clinical focus on understanding the effects of hypoglycemia, especially in children. Very little is published on the impact of hypoglycemia in this population. We aimed to review the existing literature on hypoglycemia in critically ill neonates and children.

Methods:

We performed a systematic review of the literature up to August 2011 using PubMed, Ovid MEDLINE and ISI Web of Science using the search terms "hypoglycemia or hypoglyc*" and "critical care or intensive care or critical illness". Articles were limited to "all child (0–18 years old)" and "English".

Results:

A total of 513 articles were identified and 132 were included for review. Hypoglycemia is a significant concern among pediatric and neonatal intensivists. Its definition is complicated by the use of a biochemical measure (i.e., blood glucose) for a pathophysiologic problem (i.e., neuroglycopenia). Based on associated outcomes, we suggest defining hypoglycemia as <40–45 mg/dl in neonates and <60–65 mg/dl in children. Below the suggested threshold values, hypoglycemia is associated with worse neurological outcomes, increased intensive care unit stay, and increased mortality. Disruptions in carbohydrate metabolism increase the risk of hypoglycemia in critically ill children. Prevention of hypoglycemia, especially in the setting of intravenous insulin use, will be best accomplished by the combination of accurate measuring techniques, frequent or continuous glucose monitoring, and computerized insulin titration protocols.

Conclusion:

Studies on hypoglycemia in critically ill children have focused on spontaneous hypoglycemia. With the current practice of maintaining blood glucose within a narrow range with intravenous insulin, the risk factors and outcomes associated with insulin-induced hypoglycemia should be rigorously studied to prevent hypoglycemia and potentially improve outcomes of critically ill children.

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Abbreviations: (BG) blood glucose, (CGM) continuous glucose monitoring, (ICU) intensive care unit, (POC) point of care

Keywords: blood glucose, blood glucose meter, epidemiology, intensive care, outcome, risk factors

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Introduction

Healthy individuals regulate blood glucose (BG) levels within a narrow range.[1] Critical illness is associated with disruptions of homeostatic mechanisms resulting in hyper- and hypoglycemia, both of which are associated with poor outcomes in critically ill neonates, children, and adults.[2–11] The practice of glycemic control with intravenous insulin in critically ill patients has brought clinical focus on understanding the effects of insulin-induced hypoglycemia, especially in children. Surveys among critical care physicians report that concern for inducing hypoglycemia limits the adoption of tight glycemic control where BG is maintained at 80–110 mg/dl.[12–14] This concern is heightened in children because of the effects of low BG on the developing brain.[15]

The body defends against hypoglycemia primarily because the brain depends on BG as its main energy source. Hypoglycemia may result in altered consciousness, syncope, seizures, and eventually coma and death. Although the brain contains enzymes that can metabolize alternate sources of fuel (e.g., lactate and ketones) when arterial BG falls below 54 mg/dl, cerebral metabolism and function decline.[16,17] The brain is quite sensitive to acute hypoglycemia, but less so to chronic glucose deprivation where it can metabolize ketones for up to 60% of its energy requirements.[18] During an acute episode of hypoglycemia, counterregulatory hormones are activated, cerebral blood flow is increased, and alternate energy sources are recruited for gluconeogenesis.[19,20] Teleologically, an endogenous glucose surge in response to an acute stressor resulting in hyperglycemia may be the way the body has developed to protect against hypoglycemia. Hypoglycemia impairs neurological function and threatens an organism's ability to have a successful "fight or flight" response. In contrast to managing and overcoming an acute environmental stressor, the critically ill patient suffers from prolonged stress. This, combined with therapies that affect glucose metabolism and the catabolic state of severe illness, likely predisposes a patient to the glycemic instability witnessed in critical illness and potentially impairs normal mechanisms for defending against hypoglycemia.[21] The immediate and long-term consequences of spontaneous and insulin-induced hypoglycemia in critical illness states are, in general, unknown.

During critical illness there is increased glucose utilization, inadequate nutrition, and decreased endogenous glucose production. Exogenous insulin can become a common cause of hypoglycemia.[22] Most of what is known about hypoglycemia and its lasting effects is based on studies of healthy volunteers or patients with diabetes. Very little is published on the impact of hypoglycemia in critically ill nondiabetic children. The objective of this article is to review the published data on the definition/epidemiology, outcomes, risk factors, and prevention of hypoglycemia in critically ill children. Data are presented for critically ill neonates and children and covers both spontaneous and insulin-induced hypoglycemia.

Method

We performed a systematic literature search of all articles up to August 2011. We searched PubMed, Ovid MEDLINE and ISI Web of Science for articles containing the terms "hypoglycemia or hypoglyc*" and "critical care or intensive care or critical illness". We limited the articles to "all child (0–18 years old)" and "English". The authors (EVSF and ELH) reviewed the abstracts and full texts of all relevant articles. Articles with data on definition/epidemiology, outcomes, risk factors, and prevention of hypoglycemia were included. References from these articles were also reviewed and new articles were included as appropriate.

We obtained 400 articles from PubMed, 277 articles from Ovid MEDLINE and 185 articles from ISI Web of Science. A total of 132 articles were used in the review.

Definition and Epidemiology of Hypoglycemia

The definition of hypoglycemia is unclear. Traditionally, researchers have separated biochemical hypoglycemia from symptomatic hypoglycemia that requires intervention.[23,24] In noncritically ill patients with diabetes, severe hypoglycemia is often defined as a BG level <60 mg/dl that is associated with loss of consciousness, seizures, administration of glucagon or intravenous glucose to treat the low BG.[25] Some argue that hypoglycemia should be defined as the lowest concentration of BG that is compatible with normal metabolism, physiology, neurological function, and outcome.[26] Definitions vary in clinical practice. One survey among neonatologists reported that hypoglycemia was defined from 20 mg/dl to 55 mg/dl.[27] In surveys of pediatric intensivists, most defined hypoglycemia as BG <40 or <60 mg/dl while some report cutoff values of <80 mg/dl.[12,13] The discrepancy in

definitions has likely affected the reported incidence of hypoglycemia in neonates and children.

The difficulty in defining hypoglycemia is, in part, due to the use of BG measurements as a surrogate for symptomatic neuroglycopenia. The use of neurological symptoms to define hypoglycemia becomes particularly problematic in critically ill patients. Sedative medications and chemical paralysis can hinder detection of mild changes in sensorium or mask seizures. Additionally, critically ill children who present with neurological symptoms often have underlying structural and biochemical abnormalities that make it difficult to attribute the symptoms to hypoglycemia.[28]

Another challenge to a clear definition of hypoglycemia is the variable effect of hypoglycemia on the central nervous system in different ages. In animal models, neonates are more protected than adult animals from neuronal injury due to low BG.[29] Normal human fasting BG level is 50–80 mg/dl in infants, 70–100 mg/dl in children and 80–110 mg/dl in adults.[1] Blood glucose of 40–45 mg/dl (considered severe hypoglycemia in older patients) may be found in 5–15% of normal newborns and may not be treated.[29]

The cause of hypoglycemia (spontaneous or insulin-induced) may alter the definition or threshold for treatment of hypoglycemia. During fasting, the brain can metabolize ketones and amino acids as its primary energy source, thereby reducing neurological damage.[18] Insulin decreases lipolysis and impairs ketogenesis depriving the brain of an alternate energy source. In healthy volunteers exposed to hypoglycemia via insulin, a fall in glucose metabolism occurs before most of the counterregulatory responses and cognitive changes occur.[30] Alterations in metabolic demand during critical illness, are likely to further impact the normal response to hypoglycemia.

The method of BG measurement also affects the significance of any chosen BG threshold. Plasma glucose is approximately 10% higher than whole BG.[29] Blood glucose measurements from point-of-care (POC) devices may be affected by numerous factors unique to the critically ill patient including hematocrit, pH and oxygen tension.[31–34] The blood compartment (i.e., capillary, venous, or arterial) from which the specimen is taken also affects BG readings.[35,36] Significant variations in definitions of hypoglycemia, detection of symptoms, and accuracy of BG measurements make clinical studies difficult and prevent a clear understanding of the incidence and outcomes of hypoglycemia.

Despite the difficulties in defining hypoglycemia, the threshold should be determined based on clinically significant outcome measures. In critically ill neonates with increased metabolic demands, BG <40–45 mg/dl is associated with abnormal neurological outcome and death.[15,37] Beyond the neonatal period, BG <60–65 mg/dl is associated with increased duration of hospital stay and death in critically ill children.[5,38]

Spontaneous hypoglycemia, with BG <40–45 mg/dl, occurs in 9.2 to 24.3% of neonates.[39–41] Insulin-induced hypoglycemia likely varies with site and individual practice, but has been reported to be as high as 29%.[39] In the pediatric intensive care unit (ICU), spontaneous hypoglycemia, with BG <60–65 mg/dl, occurs in 7 to 9.7% of children[5,7,42] while insulin-induced hypoglycemia may occur in as much as 33% of children.[42–45]

Outcomes of Hypoglycemia

Studies investigating outcomes of hypoglycemia in critically ill children are limited by their retrospective and observational nature. It is difficult to establish whether hypoglycemia is causal to an outcome of interest or merely a marker of severity of illness despite the pathophysiological plausibility of the association.[5,15]

Spontaneous hypoglycemia is associated with worse outcomes both in critically ill neonates and children. In critically ill neonates, BG <40–45 mg/dl is associated with abnormal neurological outcome and death with diffuse basal ganglia or thalamus hyperechogenicity suggestive of neuronal injury in preterm neonates.[15,37,46] The clinical significance of these lesions is unknown. Hypoglycemia in preterm infants is also associated with a longer stay in the ICU.[47] In multivariate analysis, the presence of hypoglycemia increased length of stay by 1.87 days. The association between hypoglycemia and neurological outcome in neonates is not consistent. Nadeem and colleagues[48] reported that in term neonates with hypoxic-ischemic encephalopathy, BG <50 mg/dl during the first 6 h of life is common in patients with worse neurological outcome. However, this was likely a reflection of the severity of the encephalopathy as the association was lost when the analysis was adjusted. Salhab and colleagues[15] reported in a similar patient population that initial BG ≤40 mg/dl is independently associated with abnormal neurological outcome. The odds ratio for abnormal neurological outcome in the presence of hypoglycemia was 18.5. Significant reductions in mental and motor development scores at 18 months were reported in preterm neonates with asymptomatic

hypoglycemia defined as BG <45 mg/dl.[49] The magnitude and incidence of developmental impairment were strongly related to the frequency of hypoglycemia. The incidence of cerebral palsy or developmental delay was increased by a factor of 3.5 when hypoglycemia was recorded on 5 or more separate days.

In critically ill children, hypoglycemia is associated with prolonged stay in the ICU and increased mortality.[5,38,50,51] Compared with euglycemic patients, children with hypoglycemia stay in the ICU for an additional 7.5 days.[38] Mortality rates are inversely related to the severity of the hypoglycemic event[5]. The odds ratio for mortality for children with BG <60 mg/dl is 2.7, while in children with BG <40 mg/dl, odds ratio for morality is 4.5.[5] Children with more than one episode of hypoglycemia (BG <60 mg/dl) have worse outcomes compared with children with a single episode of hypoglycemia.[5] In postoperative cardiac patients, intraoperative hypoglycemia is associated with increased composite outcome of mortality and infection.[52]

The short- and long-term outcomes of insulin-induced hypoglycemia in critically ill children are unknown. Although impairment in ketogenesis and an inability to present with typical neurological symptoms while sedated may lead to more frequent hypoglycemia, critically ill children are closely monitored in the ICU and may not be hypoglycemic for prolonged periods of time. In the only randomized trial on tight glycemic control in critically ill children, Vlasselaers and colleagues[53] reported that hypoglycemia (which occurred in 25% of the intensively managed cohort) was not associated with mortality after adjusting for duration of stay in the ICU. Similarly, Kyle and colleagues[54] reported that BG <40 mg/dl in a cohort of children who received intravenous insulin for hyperglycemia was associated with multiple organ dysfunction but not with increased mortality. It is possible that insulin-induced hypoglycemia may lead to transient impairment in cognition as seen in patients with diabetes.[55] However, this will be difficult to determine in critically ill children. There is a planned post-study assessment of neurocognitive function in the participants in the study by Vlasselaers and colleagues. This will add important insight to the neurological effects of glycemic control specifically in children with insulin-induced hypoglycemia.

Risk Factors for Hypoglycemia

The body tightly regulates BG levels. Once exogenous glucose sources enter the circulation, insulin is secreted to facilitate entry of glucose into most cells in the body. Excess BG is converted into glycogen and stored in the liver. When exogenous glucose sources decrease, counterregulatory hormones, particularly glucagon, cortisol, growth hormone, and epinephrine, increase BG levels by activating glycogenolysis from the liver and stimulating gluconeogenesis from fats and protein.[20] Impairment or dysfunction in any segment of these pathways places the patient at risk for hypoglycemia.

Preterm,[56–60] small for gestational age,[59] low birth weight,[61,62] and discordant twin neonates[63,64] are at highest risk for hypoglycemia. Minimal glycogen and fat stores impair the preterm neonate's ability to maintain adequate BG levels. In preterm infants, cesarean section, intrauterine malnutrition, hospitalization in the neonatal ICU, and gestational age between 30 and 33 weeks are independent risk factors for development of BG <40mg/dl.[65] Infants of mothers with diabetes, particularly when the diabetes is poorly controlled, also comprise a large proportion of neonates at risk for hypoglycemia.[66–70] Critical illness such as asphyxia and sepsis increases the likelihood of hypoglycemia.[71–73] A hyperinsulinemic state is thought to occur in these situations because of cytokine release.[74] Similarly, tumors that produce insulin such as nesidioblastosis cause persistent hypoglycemia.[75–77] Inborn errors of metabolism (e.g., congenital adrenal hyperplasia)[78] and genetic syndromes (e.g., Beckwith Wiedeman syndrome)[79] also predispose the neonates to low BG.

The risk factors for hypoglycemia in critically ill children are similar to those of neonatal patients. They include malnutrition (especially in developing countries),[80,81] abrupt discontinuation of parenteral nutrition,[82] and liver dysfunction including inborn errors of metabolism that deprive the body of glucose stores.[83,84] Additional risks include disorders of the hypothalamic-pituitary-adrenal axis,[85–87] therapeutic or recreational drugs,[88–95] sepsis,[96,97] malaria,[98–103] and shigella.[81] Finally, hypoglycemia is also common in children <1 year old,[11] with higher severity of illness,[11] and on mechanical ventilation and/or vasopressor support.[5]

Exogenous insulin can be a strong risk factor for hypoglycemia. In the trial by Vlasselaers and colleagues,[10] hypoglycemia was significantly higher in the intervention group that received an insulin infusion—25% compared to 1% in the control group. In the adult ICU experience, large single and multicenter studies on glycemic control have documented significantly higher rates of hypoglycemia in the intensely managed versus conservatively managed groups.[104] Interestingly, there are data to

suggest that glycemic control can be practiced without increasing hypoglycemia. In the experience of many centers that use regular insulin administration to treat hyperglycemia,[42,44,45,105] the incidence of hypoglycemia appears to be lower than rates of spontaneous hypoglycemia in similarly ill populations.[5] Perhaps if performed properly, one unintended consequence of regimented approaches to detect and manage hyperglycemia is to decrease the incidence of hypoglycemia. Currently, there are no data that delineate the risk factors for insulin-induced hypoglycemia in the setting of tight glycemic control in critically ill children.

Prevention of Hypoglycemia

Presupposing that hypoglycemia is causally related to the adverse outcomes with which it is associated and that maintaining BG above a threshold will minimize these outcomes, prevention of hypoglycemia becomes essential. Available literature neither provides proof that hypoglycemia causes increased mortality and morbidity nor that prevention of hypoglycemia improves outcomes. However, in view of the biological plausibility of the association and the low risk with the intervention,[29] it is prudent to take measures to prevent hypoglycemia in critically ill neonates and children.

Hypoglycemia in critically ill neonates and children is typically asymptomatic and oftentimes detected in routine blood testing. In fact, the incidence of critical illness related hypoglycemia may be very much underestimated as most reports are retrospective and rely on sporadic laboratory assessments. Thus, routine screening is suggested for patients at high risk of developing hypoglycemia.[28,29,106] Due to the ease of use and rapidity of results, POC devices for BG are employed in a large number of ICUs. Although seemingly straightforward, multiple factors affect the accuracy of POC devices.[31,32,35,107–113] In addition, inaccuracies are greater in the hypoglycemic range.[31,32,35,109,112] Glucose meters (a type of POC device) tend to overestimate BG compared to laboratory measurements, which is considered the gold standard. In a study in a neonatal ICU, using a cutoff of 47 mg/dl, the sensitivity of a BG meter in detecting laboratory confirmed BG <47 mg/dl was only 52%.[31] Sensitivity increased to 100% when the cutoff was increased to 68 mg/dl. However, this increased the false positive rate from 9 to 88%.

Intravenous insulin administration requires frequent BG measurements to ensure safety. Clinical practice commonly utilizes POC devices for this purpose. This practice is limited by the accuracy of the device and increased nursing work load due to repeated blood draws. Continuous glucose monitoring (CGM) can potentially obviate these limitations. Continuous glucose monitoring devices measure interstitial glucose levels and produce a reading every few minutes. Substantial experience in the use of CGM has been gained in patients with diabetes.[114–119] In this patient population, investigators found a decrease in both the duration of hypoglycemia and in hemoglobin A1c values for patients randomized to the use of CGM.[114] The utility of CGM has also been studied in critically ill children.[105,120–125] In general, investigators conclude that CGM is safe and reasonably accurate, but may increase nurse workload.[105] Reported glucose values tend to be lower with CGM devices than blood levels, particularly in the hypoglycemic range.[121,126] Branco and colleagues, however, noted CGM device values to be significantly higher than blood, particularly at BG <75 mg/dl.[125] Discrepancies in readings were also more common in children with large base deficits and those being actively cooled. Continuous glucose monitoring can decrease hypoglycemia, however, screening thresholds must be determined to maximize the efficacy of the device.[105] It may be that the most substantial utility of CGM in ICUs is its ability to track and display trends, and thus serve as an early warning system to trigger routine, more accurate testing. Currently, the Food and Drug Administration has approved CGM only for children older than 7 years old in outpatient settings.

In the setting of tight glycemic control, the use of algorithms and protocols is associated with a decreased incidence of hypoglycemia.[10,42,44,45,127–129] Frequent BG measurements, protocol compliance, and a higher BG target are also associated with a decrease in hypoglycemia.[48,128,130] Various protocols exist that adjust insulin infusions for hyperglycemic critically ill children.[42,44,45,128] Most protocols account for current BG value, rate of change in BG, and current insulin rate. The ideal insulin infusion protocol would also account for changes in patient nutrition and administration of medications and would adapt to patient specific data.

Due to the number of factors involved, computerized protocols tend to be superior to paper protocols in preventing hypoglycemia and achieving the desired BG level.[44,128,130] Compliance with protocol recommendations is associated with increased success at achieving clinical targets. Delays in the timing of glucose measurements are associated with increases in hypoglycemia and electronic reminders can minimize this risk. Computer protocols can automatically track clinician protocol compliance

and are associated with increased compliance.[44,130–132] Computerization of a paper protocol can also reduce insulin titration errors.[132]

Prevention of hypoglycemia in the critically ill child is probably best accomplished by the combination of accurate measuring techniques, frequent or continuous BG monitoring, and computerized insulin titration protocols that can quickly incorporate and adjust to several patient specific factors. It is highly likely that integration of some form of CGM linked directly or indirectly to insulin infusion (i.e., the "artificial pancreas" concept) will not only enhance detection and management of critical illness hyperglycemia, but also improve the prevention of hypoglycemia.

Summary

Hypoglycemia is a significant concern among neonatal and pediatric critical care specialists. While experimental data confirm the neurological effects of hypoglycemia, available clinical data do not confirm a causal relationship between hypoglycemia and clinically significant adverse outcomes, such as neurological dysfunction, prolonged stay in the ICU, or increased mortality. The uncertainty in the association makes it difficult to define hypoglycemia. However, based on the reported associations, we suggest using a cutoff of <40 mg/dl in neonates and <60 mg/dl in children. We further suggest that in children, episodes of severe hypoglycemia defined as BG <40 mg/dl be reported due to the obvious continuum in critically ill patients. At this time, it is unclear whether the same threshold values should be used for insulin-induced hypoglycemia, but using a standardized schema in reporting will facilitate understanding and progress in this field. Currently, data suggest that outcomes are similar between insulin-induced and spontaneous hypoglycemia. In the absence of definitive data on causality, it is prudent to institute measures to prevent hypoglycemia. Patients at risk for low BG should be monitored closely. Use of CGM and computerized protocols during administration of intravenous insulin may decrease the incidence of hypoglycemia in critically ill children.

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