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SYMPOSIUM

An Overview of Hypoglycemia in the Critically Ill

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Abstract

Hypoglycemia is a common and serious problem among patients with diabetes mellitus. It is also perceived as the most important obstacle to tight glucose control using intensive insulin therapy in critically ill patients. Because glucose is an obligatory metabolic fuel for the brain, hypoglycemia always represents an emergency that signals the inability of the brain to meet its energy needs. When left untreated, hypoglycemia can result in permanent brain damage and ultimately, death. In the context of critical illness that limits endogenous glucose production and increases glucose utilization, inadequate nutrition, or insufficient provision of glucose, intensive insulin therapy is the most frequent cause of hypoglycemia. Neurogenic and neuroglycopenic symptoms of hypoglycemia can remain unknown because of the underlying critical illness and sedation. Thus, close and reliable monitoring of the glycemic level is crucial in detecting hypoglycemia. In prospective randomized controlled studies comparing the effects of two glucose regimens, intensive insulin therapy aimed to reach strict glucose control (<110 mg/dl) but increased the incidence of severe hypoglycemia (<40 mg/dl) by four- to sixfold. Severe hypoglycemia is statistically associated with adverse outcomes in intensive care unit patients, although a direct causal relationship has not been demonstrated.

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Introduction

Hypoglycemia is the limiting factor in improving or maintaining glycemic control in diabetes.[1] In patients with type 1 diabetes, the plasma glucose level is below 50–60 mg/dl 10% of the time. Improving chronic outpatient glycemic control increases the incidence of symptomatic hypoglycemia (average of two episodes per week) and of severe hypoglycemia (approximately once a year).[2,3] An estimated 2–4% of deaths of people with type 1 diabetes have been attributed to hypoglycemia.[4,5]

Spontaneous episodes of severe hypoglycemia are rare during the management of critically ill patients (usually observed in less than 1.5% of patients)[6,7] and are observed mainly during fulminant hepatic failure and/or overt adrenal failure during septic shock, especially in patients with severe comorbidities (malnutrition, liver cirrhosis, chronic renal failure). Since the introduction of the strict glycemic control strategy in intensive care units (ICUs),[8] hypoglycemia has become a daily concern during the management of critically ill patients.

Absolute or relative insulin excess, with inadequate or interrupted nutritional support and/or insufficient provision of exogenous glucose, together with features of

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Abbreviations: (ICU) intensive care unit, (FFA) fatty free acids, (RCT) randomized control trial

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critical illness that limit endogenous glucose production and accelerate glucose utilization are the fundamental causes of hypoglycemia in the ICU.[9]

Moreover, achieving and maintaining normoglycemia are the result of a complex process (blood/capillary sampling, glucose measurements, reading of an algorithm or recording the glycemic value in a computer, change of the insulin dose, supervision of the enteral or parenteral nutritional support) in which the human factor is omnipresent.[10] The occurrence of occasional human errors or inability to follow the algorithm because of workload can also represent additional risks for hypoglycemia. Second, other circumstances contributing to the occurrence of hypoglycemia (such as renal and/or hepatic failure, adrenal insufficiency, antibiotic treatment with a quinolone) can be present.[9]

Definition of Hypoglycemia

A plasma glucose concentration below 70 mg/dl is the most common threshold used to define hypoglycemia.[11] Hypoglycemia could be considered symptomatic and documented (typical symptom of hypoglycemia with a measure of glycemia below 70 mg/dl); probably symptomatic (symptom of hypoglycemia without a glucose measurement); or biological (measure of glycemia below 70 mg/dl without symptoms).[12] In general terms, hypoglycemia is considered to be severe if the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitation actions is required. These episodes may be associated with neuroglycopenia symptoms.[12]

In most of the studies of glucose control in the ICU, only the incidence of severe hypoglycemia—defined arbitrarily as values below 40 mg/dl, regardless of whether associated symptoms are present—is reported.[8]

Physiological Response to Hypoglycemia

Physiological responses to hypoglycemia have been studied using a hypoinsulinemic glucose clamp technique.[13,14] When blood glucose decreases to a concentration of about 80 mg/dl, inhibition of insulin secretion occurs, resulting in a decrease in the use of peripheral glucose and in removal of hepatic gluconeogenesis blockade.

When blood glucose decreases below 65 mg/dl, the secretion of glucagon, the most important counterregulatory hormone, by pancreatic α cells rises. Glucagon increases the hepatic production of glucose (both gluconeogenesis and glycogenolysis), thereby maintaining an increasing blood glucose concentration. Epinephrine, which is secreted in the same range of the blood glucose level, plays a negligible role in the rise of blood glucose, except in the absence of glucagon. Epinephrine raises blood glucose by increasing both glycogenolysis and gluconeogenesis.

The decrease in insulin concentration and the increase in epinephrine allow free fatty acids (FFA) to be mobilized from adipose tissue. When the insulin/glucagon ratio decreases, FFA are converted at the hepatic level into ketone bodies, which can be used by the brain as an energy source. The persistence of insulin secretion (insulinoma or insulin intake), however, prevents lipolysis and the production of ketone bodies by the liver.[15]

The Brain and Hypoglycemia

Glucose is an obligatory metabolic fuel for the brain, which cannot synthesize glucose or store substantial amounts of glycogen.[16] The glucose concentration in the brain normally shows a linear relationship to blood concentration with normal blood glucose levels ranging between 70 and 130 mg/dl and the corresponding normal brain concentrations ranging from roughly 14 to 41 mg/dl.[17,18] However, the rate of brain glucose metabolism outstrips transport capacity at low blood glucose levels, resulting in a brain glucose concentration near zero when the blood glucose concentration falls below 36 mg/dl.[19] Thus, neuroglycopenia generates a functional brain failure, which can result in irreversible brain injury in the case of profound and prolonged hypoglycemia.

Glucose is not the only fuel that can be utilized by the brain. The noninjured brain can also utilize ketone bodies, particularly during starvation.[20] *In vivo*, about 50% of glucose leaving the capillaries is captured directly by the neurons and the other half by the astrocytes. Experimental data suggest a continuous transfer of intermediate metabolites such as lactate from astrocytes to the neurons.[21]

During severe hypoglycemia, glycogen stores appear to play a special role in maintaining brain function.[22] Studies suggest that increasing brain glycogen stores increases the latency to electroencephalogram isoelectricity and protects neuronal activity.[23–25] Several observations contribute to the hypothesis that astrocyte glycogen breaks

down to lactate, which is exported to the extracellular space and then taken up by neurons or axons as an aerobic fuel.[26–28] In this way, neurons and axons operate normally if lactate is substituted for glucose as fuel.[29] Moreover, in experimental conditions of aglycemia, interruption of neuronal lactate uptake is associated with an accelerated neuronal functional failure.[23,30]

In animal models or in human autopsy studies of patients dying after severe hypoglycemia, the most sensitive neuronal populations are the superficial layers of the cortex, the hippocampus, the caudate nucleus, and the subiculum.[31–33] More recent studies indicate that mild, recurrent hypoglycemia can cause dysfunction in the hippocampus even in the absence of cell death.[34]

Hypoglycemic-induced neuronal death is not a direct result of energy failure. It results from a sequence of events initiated during profound, prolonged hypoglycemia, such as an extracellular release of excitatory amino acids (glutamate and aspartate)[35] and of zinc.[36,37] Activation of the postsynaptic glutamate receptor and postsynaptic zinc accumulation induce a variety of mechanisms leading to neuronal death.[38–41]

Moreover, recent experimental studies provide evidence that hypoglycemic superoxide production and neuronal death are increased during glucose reperfusion.[42] The appropriate clinical extrapolation of these data, obtained under extreme hypoglycemic conditions rarely observed in clinical practice, is not entirely clear. Even if these data suggest avoidance of hyperglycemia, it would be reasonable to raise the glucose level above 70 mg/dl promptly.[43]

The Heart and Hypoglycemia

Myocardial cells can use either fatty acids or glucose oxidation as their main energy fuel.[44] Under normal conditions, the oxidation of fatty acids is most prominent. However, the myocardium has a remarkable ability to switch between carbohydrate and fat fuel sources. During physical exercise, starvation, or in patients with diabetes, the use of fatty acids is predominant. In dilated or hypertrophic cardiomyopathy or during ischemia or hypoxia, myocardium preferentially uses glucose as an energy substrate.[45] Cardiac rate and rhythm disturbances, including sinus tachycardia,[46,47] sinus bradycardia (<40 beats/min), and ventricular and atrial ectopy,[48] have been observed during acute insulin-induced hypoglycemia or during nocturnal hypoglycemia in type 1 diabetes.

Ventricular repolarization abnormalities appear to be the main feature observed during episodes of hypoglycemia. Corrected QT interval prolongation and increased QT dispersion have been demonstrated during acute insulin-induced hypoglycemia in healthy subjects,[49,50] in patients with type 1[51] or type 2 diabetes,[52] or during nocturnal hypoglycemia in type 1 diabetes.[48,53] These abnormalities are mainly linked to hypoglycemic-induced sympathoadrenal stimulation and are prevented by selective β blockade.[50] These proarrhythmogenic abnormalities may be involved in the "dead-in-bed" syndrome in type 1 diabetes patients.[48–51]

Clinical Signs Related to Hypoglycemia

The drop in glucose concentration results in a number of symptoms linked to activation of the global autonomic nervous system.[54] Symptoms linked to neuroglycopenia are the direct result of the lack of brain metabolic energy. These symptoms include feelings of warmth and fatigue, as well as formal thought disorders, behavioral changes (often believed to be intoxication), and emotional lability. Focal signs such as diplopia or hemiparesis are rarely seen. Seizures can occur.[54,55] Coma may result from values below 40–50 mg/dl.[56]

Thus, it appears that a patient in the ICU is in a precarious situation when a hypoglycemic event occurs due to the lack of specificity of warning signals and the inability to assess the slightest change in neurological status if the patient is under deep sedation. Thus, instituting an insulin therapy, irrespective of the desired blood glucose level, requires that the medical team be sensitive to symptoms suggestive of hypoglycemia and its management. The end purpose is the same, i.e., screening and correction of hypoglycemia at very short notice. This supposes that blood glucose measurements can reliably identify low blood glucose levels.

Glucose Measurements in the ICU Setting

The measurement of glucose is extremely complex.[57] First, glucose measurements can be performed in whole blood, plasma, or serum. Second, blood may be arterial, capillary, or venous. Third, different enzymatic reactions are available to determine the glucose level: glucose oxidase, glucose dehydrogenase, and hexokinase glucose. Fourth, other variables could interact with the glucose measurement: PaO_2, pH, hematocrit, and some medications such as paracetamol (acetaminophen).[58–60] Several ICU studies have been performed to assess the degree of correlation between laboratory glucose

measurements (using a hexokinase method considered as the gold standard) and glucose measurements using either bedside glucometers (from capillary or arterial blood samples) or blood gas/chemistry analyzers located in the ICU.[61–71]

The results of these studies have demonstrated that the use of glucometers, especially from capillary blood samples, was associated with an increased frequency of falsely elevated glucose readings. Only the study performed by Kanji and colleagues,[65] in which patients received an intensive insulin infusion to achieve normoglycemia, provided direct assessment of this problem in situations of hypoglycemia (<82 mg/dl). Indeed, glucose measurements were overestimated with the use of glucometers, respectively, in 29% of cases (11 glucose readings from 38) with finger stick samples and in 19% with arterial blood samples. In comparison, masking true hypoglycemia was not observed with use of a blood gas/chemistry analyzer.[65]

In clinical critical care practice, these results prompt us not to recommend using finger stick measurements to diagnose hypoglycemia. At a minimum, they encourage consideration of the glucose measurement technique when deciding upon thresholds of hypoglycemia for stopping insulin infusions in the ICU. In clinical ICU research, to obtain an accurate value for the incidence of hypoglycemia, hypoglycemia detected with a bedside device must be corroborated in the laboratory.

Incidence of Hypoglycemia and Strict Glucose Control Strategy

In some studies, hypoglycemia is described as the number or percentage of measurements below a certain blood glucose level.[72,73] Nevertheless, this overall criterion has no direct clinical relevance. More accurately, hypoglycemia, in other studies, is represented as the number or percentage of patients who experience at least one measurement below a predefined threshold.[7,8,74–76]

However, different values have been used to define a hypoglycemic event varying from <40 to <82 mg/dl.[6,77] In a cohort study recording the lowest blood glucose level observed during the first 24 hours of an ICU stay, the incidence of hypoglycemia varied from 13.8% with a threshold below 82 mg/dl to less than 1.5% with a threshold below 44 mg/dl.[6]

More often, severe hypoglycemia is defined most commonly as a blood glucose level below 40 mg/dl. An increased incidence of severe hypoglycemia using the intensive insulin therapy strategy has been clearly demonstrated. This indisputable fact is observed in all randomized control trials (RCTs) comparing the impact of maintaining glycemia at two different levels: one considered as tight (below 110 mg/dl) and the other as conventional (below 180 or 200 mg/dl).[7,8,74–76] Thus, the severe hypoglycemia incidence reached 5.1,[8] 18.7,[76] 17,[75] 9.8,[74] and 6.8%[7] in the tight blood glucose control group versus, respectively, 0.8, 3.1, 4.1, 2.7, and 0.5% in the conventional glucose control group. During use of an intensive insulin strategy, the risk of severe hypoglycemia, assessed by the proportion of patients who experienced at least one episode of hypoglycemia, appeared multiplied by a factor of 5.1 or 6 in two recent meta-analyses.[78,79]

In contrast, the number of episodes of hypoglycemia per patient may not be increased by intensive insulin therapy: severe hypoglycemia occurred once in 75% of patients who experienced severe hypoglycemia in the intensive insulin group and in 81% of patients in the conventional group.[8,75,76] Moreover, the mean blood glucose level recorded during these severe hypoglycemic episodes (around 30 mg/dl) is similar irrespective of the glucose target desired.

Impact of the Occurrence of Hypoglycemia on Mortality and Morbidity in Critical Illness

This is a critical issue, as can be seen from the premature cessation of two recent multicenter RCTs because of, among other things, an unacceptably higher incidence of hypoglycemia in the insulin-intensive strategy group. It is associated with several important questions.

Is the Hypoglycemic Episode Directly Responsible for an Increased Risk of Death in Critical Illness?

The direct mortality associated with prolonged and profound hypoglycemia in two cohort studies of patients with insulin overdose ranged from 2.7 to 5%.[56,80] Based on results of three published RCTs on intensive insulin strategy, one case–control trial and two recent large cohort studies in critically ill patients, a strong association indisputably exists, after adjustment in multivariate analysis, between the occurrence of at least one episode of hypoglycemia and worse prognosis. Thus, the risk of death in the case of hypoglycemia appeared to be increased significantly by a factor of, respectively, 3.2,[8] 2.9,[76] 3.3,[75] 2.3,[81] 2.3,[82] and 1.4.[6]

However, in another case–control study performed from a cohort of patients receiving insulin infusion to maintain a glucose target between 80 and 140 mg/dl,[83] the occurrence of hypoglycemia was not associated with an increased risk of mortality whatever the variables introduced into the multivariate analysis.[84] These data are the most consistent findings that could support the detrimental effect of hypoglycemia, as a randomized trial of severe hypoglycemia will never be performed, for obvious reasons.

Clinical symptoms potentially linked to occurrence of hypoglycemia appeared rare. In the first RCT performed in surgical ICUs, two of the recorded hypoglycemic episodes were accompanied by sweat and agitation.[8] In the RCT performed in the medical ICU by Van den Berghe and colleagues, no symptom had been recorded during severe hypoglycemia.[76] In the Volume Substitution and Insulin Therapy in Severe Sepsis study, 26 of the 54 episodes of severe hypoglycemia were classified as serious adverse events (but without details concerning the occurrence of clinical events) and 19 of them were considered as life-threatening (even if severe hypoglycemia was not found to result directly in death).[75] In the cohort of 154 patients who had experienced one episode of hypoglycemia in a case–control study in which cases were matched by ICU length of stay prior to hypoglycemia as compared to other studies that based it on other variables such as severity of illness, presence of diabetes, and age, Vriesendorp and colleagues reported one case of refractory seizure and two cases of coma in which a causal role of hypoglycemia seemed likely, but could not be fully established.[84] Thus, it appears that the majority of severe hypoglycemic episodes observed during insulin infusion in the ICU, whatever the desired target glycemia, were just "biological" hypoglycemia. Nevertheless, potential "hypoglycemic" neurological symptoms could be masked.

The other main variable involved in the severity of hypoglycemia—duration of severe hypoglycemia—was not provided in the studies cited earlier. Nevertheless, in the Glucontrol study, the duration of severe hypoglycemic episodes was increased significantly in the intensive insulin group, 97 minutes (SD ± 7) versus 75 (SD ± 13) in the conventional group.[74]

In awaiting the specific analysis of the severe hypoglycemia recorded in the Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation study, the direct contribution of hypoglycemic episodes (especially those linked to insulin infusion) to poor outcomes in critical illness remains unclear, despite the statistical association between the occurrence of hypoglycemia and a higher risk of mortality.

What Is the Impact of Hypoglycemic Episode on Morbidity in Critical Illness?

Patients who survive after a critical illness routinely present with chronic neurocognitive dysfunction (including impairments of memory, attention, or executive functions) and/or psychiatric sequale (confusion, depression, anxiety).[85,86] The impact of hypoglycemia on neuro-psychiatric recovery has not been specifically evaluated. Nevertheless, reversible abnormalities with attention have been described after the performance of a hypoglycemic stress (glucose level around 30 mg/dl).[87] Of note, however, during a long-term follow-up of ambulatory patients with type 1 diabetes, development of functional cognitive impairment did not appear to be linked to the frequency of hypoglycemic episodes.[88]

Other late neurological sequelae, such as coma and epilepsy, were not recorded in the prospective Leuven trials. When pooling data of the two RCTs performed in Leuven, only three patients who experienced severe hypoglycemia (all were in the intensive insulin group) presented with coma or epilepsy prior to hypoglycemia.[89]

Conclusion

The diagnosis of hypoglycemia in critically ill patients appears to be a challenge. Bedside glucose analyzers are often not reliable at the low ranges of glycemia, and hypoglycemia-related neurological signs may be masked.

Whether spontaneous or linked with insulin infusion, the occurrence of hypoglycemia in critical illness, especially severe hypoglycemia, is associated with a poor prognosis without clear identification of the reason for this higher mortality.

Not surprisingly, intensive insulin strategy aiming to achieve "normoglycemia" is accompanied by an increased incidence of severe hypoglycemia. Because of its potentially harmful and life-threatening consequences, hypoglycemia represents the main limit to the development of a tight blood glucose control strategy in critical illness.

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