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Hypoglycemia in Critically Ill Patients

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1. Introduction

Dysglycemia is common in critically ill patients. Both hyperglycemia and hypoglycemia are independent risk factors for increased morbidity and mortality. Hypoglycemia severity may even have a 'dose-response' relationship with increased mortality(Bagshaw et al., 2009). Acute hypoglycemia induces a systemic, counter-regulatory stress response that leads to an increase in blood norepinephrine, epinephrine, glucagon, growth hormone, and cortisol concentrations. Risk factors that are associated with the occurrence of hypoglycemia in ICU patients include severity of illness, strict glucose control, continuous veno-venous hemodialysis, decrease of nutrition without adjustment for insulin infusion, a prior diagnosis of diabetes mellitus, sepsis, and need for inotropic support (Arabi et al, 2009;Krinsley & Grover, 2007;Vriesendorp et al. ,2006).

The association between hyperglycemia and mortality seems population dependent, with the strongest association in patients in the cardiac, cardiothoracic and neurological ICU(Whitcomb et al., 2005). During acute illness, hyperglycemia might exert an even more deleterious effect on ICU patients without diabetes than among patients with diabetes(Capes et al., 2000;Krinsley 2006;Rady et al., 2005). Unlike nondiabetic patients, diabetic patients show no clear association between hyperglycemia during intensive care unit stay and mortality and markedly lower odds ratios of death at all levels of hyperglycemia. These findings suggest that, in critically patients with diabetes mellitus, hyperglycemia may have different biological and/or clinical implications(Egi et al., 2008).

Recently, variability of glucose concentrations has been identified as an additional factor that may contribute to the mortality and morbidity of dysglycemia. A retrospective evaluation of over 7000 patients identified glycemic variability, defined as the standard deviation of each patient's mean glucose level during ICU stay, as a stronger predictor of mortality than hyperglycemia(Egi et al., 2006). High glucose variability during ICU stay was associated with increased mortality in patients without diabetes, even after adjustment for severity of illness and mean glucose concentration(Krinsley 2009). In contrast, there was no independent association of glucose variability with mortality among patients with diabetes. Glucose variability contributes to ICU mortality and in-hospital death by increasing oxidative stress, neuronal damage, mitochondrial damage, and coagulation activation.

The relation between glucose concentration and outcome is complex and not linear. The interaction between glucose concentrations and outcome may arise from independent and synergistic domains of glycemic control including central tendency (such as mean and

median glucose values), variability and the minimum glucose value (Mackenzie et al., 2011). Using these different metrics of glycemic control, a population-specific relationship between metrics of outcome was demonstrated in patients in a surgical, trauma, cardiac and neurological ICU. This relationship had a dose response component with an n-shape curve in neurological ICU patients, suggesting a survival advantage during hyperglycemia in these patients.

Strict glycemic control may improve morbidity and mortality in critically ill patients. Intensive glucose control is however associated with a higher incidence of hypoglycemia compared to conventionally treated patients. This increased risk of hypoglycemia may limit the use of strict glucose control in critically ill neurological patients, since hypoglycemia is a well known cause of secondary brain injury. In this review we will describe the different aspects of dysglycemia and glycemic control in critically ill patients, with a special emphasis on the critically ill neurological patients.

2. Glucose homeostasis in critically ill patients

Glucose homeostasis is a physiologically well-balanced mechanism depending on coordinated and simultaneously ongoing processes involving insulin secretion by the pancreas, hepatic and renal glucose output and glucose uptake by splanchnic (liver and gut) and peripheral tissues. Cellular uptake of glucose occurs via insulin- or noninsulin-dependent mechanisms. The noninsulin-dependent pathway is the major mechanism of glucose uptake in the basal state, accounting for 75-85% of the total post-prandial glucose uptake and is mainly directed at the brain(Gottesman et al., 1983).

The brain plays a central role in the orchestration of the changes in blood glucose and the appropriate counterregulatory responses (reviewed in (Watts & Donovan, 2010)). Some neurons possess specialized mechanisms that allow them to act as glucosensors and alter their firing rates with fluctuating ambient glucose concentrations. These neurons are predominantly located in the hypothalamus and hindbrain. Important glucosensing elements are also present in the hepatic portal/mesenteric vein, gut, carotid body and oral cavity. Information from the glucosensing elements is processed by neurons in the hypothalamus and hindbrain. These neurons regulate the counterregulatory responses and provide direct input to the appropriate neuroendocrine motor and preganglionic neurons in the hypothalamus, hindbrain, and autonomic ganglia. Their output in turn controls and/or modulates effector cells in the adrenal medulla (chromaffin cells), anterior pituitary (corticotopes and somatotropes), and pancreatic islets (α- and β-cells).

Severe illness induces a stress response with alterations in the glucose metabolism including enhanced peripheral glucose uptake and utilization, hyperlactatemia, increased glucose production, depressed glycogenesis, glucose intolerance, and insulin resistance(Mizock, 1995). Stress hyperglycemia is caused by a highly complex interplay between counterregulatory hormones such as cortisol, epinephrine, norepinephrine and glucagon, leading to an increase in hepatic and renal glucose production and insulin resistance (reviewed in (Dungan et al., 2009)). The hepatic gluconeogenesis that is induced by glucagon, cortisol and epinephrine is the key source of glucose production. The kidney is responsible for approximately 20% of the glucose production under resting conditions(Meyer et al., 2002). During stress, however, cathecholamines can increase the renal contribution to glucose production up to 40% by increasing substrate availability and the gluconeogenic efficiency of the kidney(Meyer et al., 2003). Glucagon increases both

gluconeogenesis and glycogenolysis in the liver, but has no effect on the kidney. Cytokines such as IL-6 and TNF-α also contribute to the synthesis of glucose by regulation of key enzymes such as glucose 6-phosphatase (G6Pase) involved in the gluconeogenesis(Blumberg et al., 1995a;Blumberg et al., 1995b). Insulin suppresses glucose release in both the liver and kidney by direct enzyme activation/deactivation, as well as by reducing the availability of gluconeogenic substrates and actions on gluconeogenic activators. Glycogenolysis and reduced glycogen synthesis in the liver probably contribute only to a small extent to the stress induced hyperglycemia.

Insulin resistance is characterized by raised plasma levels of insulin, organ-specific alterations in glucose utilization, and impaired insulin-mediated uptake(Brealey & Singer 2009). The insulin resistance occurs at several levels and is mainly driven by the inflammatory response. TNF-α can activate protein kinase B, resulting in phosphorylation of the insulin receptor thereby reducing the glucose uptake(Fan et al., 1996;Ueki et al., 2004). In addition, a number of animal models measured a significant reduction in the number of insulin receptors(McCowen et al., 2001).

3. Glucose in critically ill neurological patients: Friend or foe?

3.1 Glucose is fuel for the brain

Under normal conditions, the human brain is an obligate glucose consumer and depends almost entirely on the availability of systemic glucose to maintain its normal metabolism. Glucose concentration in brain normally shows a linear relationship to blood concentrations with normal human blood glucose levels ranging between 70-128 mg/dL and the corresponding normal brain concentrations ranging from roughly 14.4-41.4 mg/dL (Gruetter et al., 1998).

Autoradiography and PET have shown that the rate of glucose consumption differs between brain regions, with higher values in grey matter, and also varies with time, with active areas capturing more glucose compared to inactive areas(Raichle & Mintun, 2006). In critically ill neurological patients the metabolic demand of the brain is increased, resulting in a relative deficiency in cerebral extracellular glucose(Bergsneider et al., 1997;Hutchinson et al., 2009).

Glucose is transported from the blood across the endothelial cells in the blood-brain barrier and across the plasma membranes of neurons and glia cells. Rapid breakdown of glucose by the brain creates a concentration gradient between the cerebrospinal fluid and the blood, resulting in a driving force of glucose towards the brain. Glucose is transported to the brain by facilitated glucose transport that is mediated by members of the glucose transporter (GLUT) protein family. Several GLUT isoforms have been identified in the brain: GLUT1 is highly expressed on endothelial cells at the blood-brain-barrier and in astrocytes, whereas GLUT3 is detected in neurons and GLUT5 in microglia (Vannucci et al., 1997).

During normal activity, glucose is the predominant energy substrate for neurons. The metabolic coupling between neurons and astrocytes preserves energy homeostasis in the brain during increased neuronal activity. Activation of neurons is accompanied by an increase in local cerebral blood flow, thus increasing the delivery of energy substrates. Glucose metabolism itself is also tightly coupled to neuronal activity: activation of astrocytes by glutamate, that is released by neurons, results in increased production of lactate by astrocytes that can be used as fuel by neurons to meet their energy demand (the astrocyte-neuron lactate shuffle)(Pellerin et al., 2007;Pellerin & Magistretti, 2004;Rothman et al., 1999). This astrocyte-neuron lactate shuffle also contributes to neurotransmitter recycling and

restoration of neuronal membrane potentials. Recent studies indicate that the human brain has the capacity to support up to 10% of its energy metabolism with lactate. Lactate in plasma can cross the blood-brain barrier through monocarboxylate transporters(Simpson et al., 2007). Plasma lactate may become a significant source of fuel in conditions of increased plasma lactate levels or when blood glucose levels are reduced, accounting for up to 60% of the energy metabolism(Boumezbeur et al., 2010).

Glycogen metabolism is also under the control of metabolic coupling. Glycogen is predominantly localized in the peripheral astrocytic processes surrounding the neuronal elements and serves as an endogenous source of energy for these cells and for neurons during extreme energy failure. Neurochemical signals from neurons and astrocytes trigger glycogenolysis. In astrocytes, glucose derived from glycogenolysis is used for both oxidative metabolism and for production of lactate(Benarroch, 2010). This lactate serves as an energy substrate for oxidative metabolism in neurons.

Since the brain relies upon plasma glucose as its primary energy source, a reduced blood glucose concentration promptly induces a complex counter regulatory response aiming at recovery of plasma glucose concentrations. Glucagon and epinephrine are released after a small decrease in glucose concentration, followed by activation of the autonomic nervous system. This hypoglycemia induced systemic stress response is accompanied by an increasing cerebral blood flow and altered cerebral metabolism with increased glycogenolysis. Depending on the duration and severity, the effects of hypoglycemia span from mild changes in EEG signals to irreversible brain injury and coma. Not all neurons are equally sensitive to hypoglycemic injury. Neurons in the cerebral cortex and the hippocampus are affected preferentially, followed by neurons in the basal ganglia and the thalamus. Neurons in the brain stem, the cerebellum, and the spinal cord are generally spared, as are glial cells and white matter tracts (Auer et al., 1989). The hypoglycemic neuronal damage is not a direct result of energy failure but mainly caused by an excitotoxic amino acid mediated increase in intracellular calcium, production of reactive oxygen species and apoptosis (Suh et al., 2007).

In acute brain injury, the hypoglycemic threshold is lower compared to normal brain and even mild hypoglycemia can induce neuroglycopenia. In patients after traumatic brain injury, arterial glucose levels < 108 mg/dL resulted in decreased brain glucose concentrations with an increased cerebral uptake of glucose(Meierhans et al., 2010). Microdialysis markers of brain metabolic distress were significantly reduced at brain glucose concentrations > 18 mg/dL, reaching the lowest levels at arterial blood glucose levels between 108-162 mg/dL. From this study it was concluded that arterial blood glucose concentrations between 108-162 mg/dL were optimal in traumatic brain injury. In addition, low brain glucose concentrations are associated with recurrent, spontaneous, spreading depolarizations in pericontusional tissue, resulting in a further reduction in brain glucose concentration and an ongoing brain damage (Feuerstein et al., 2010;Parkin et al., 2005).

3.2 Glucose is toxic to the brain

Stress-related hyperglycaemia, previously considered to be a protective physiological response to meet the increased demands of an injury, is associated with a poor outcome in critically ill patients. This association of poor outcome and hyperglycemia has been consistently confirmed across multiple studies and different disease entities such as traumatic brain injury (Jeremitsky et al., 2005;Lam et al., 1991;Rovlias & Kotsou, 2000;Salim

et al., 2009), intracranial hemorrhage (Fogelholm et al., 2005;Godoy et al., 2008;Godoy et al., 2009;Godoy & Di, 2007;Kimura et al., 2007;Passero et al., 2003) and subarachnoid hemorrhage (Badjatia et al., 2005;Frontera et al., 2006;Kruyt et al., 2008;Kruyt et al., 2009;Lanzino et al., 1993).

Hyperglycemia is associated with many detrimental effects, including reduced immune function, increased inflammation and coagulation, and modulation of the endothelium. Plasma concentrations of pro-inflammatory cytokines are increased during hyperglycemia, while insulin reduces the pro-inflammatory cytokine response and restores the pro- and anti-inflammatory balance (Turina et al., 2005). Glucose increases basal TNFα and IL-6 production in human monocytes *in-vitro* (Morohoshi et al., 1996). Similarly, a glucose-dependent increased production of TNFα by peripheral blood cells *in-vitro* after stimulation with lipopolysaccharide was measured, whereas glucose does not influence the production of the anti-inflammatory cytokine IL-10 (Hancu et al., 1998). *In-vivo* induced hypoglycaemia in hypoglycaemic human clamp models resulted in a down-modulation of lipopolysaccharide -induced TNFα synthesis(de Galan et al., 2003). Hyperglycemia increases the expression of tissue factor, which has both proinflammatory and procoagulant functions(Brealey & Singer, 2009). Hyperglycemia induces endothelial dysfunction through several damaging pathways, including the polyol/sorbitol/aldose reductase pathway, the protein kinase C pathway, the accumulation of non-enzymatic glycation end products and by increased oxidative stress, ultimately leading to increased expression of endothial cytokines and adhesion molecules (van den Oever et al., 2010). Insulin infusion restores normoglycemia in critically ill patients and improves and restores host defence, haemodynamics and coagulation abnormalities.

The deleterious effects of acute hyperglycemia on brain injury has been demonstrated in a large number of animal studies (reviewed in (Ergul et al., 2009)). Hyperglycemia increases infarct volume in focal models of ischemia and aggravates necrosis in global ischemia/reperfusion models. In addition, hyperglycemia contributes to the vascular damage during ischemia/reperfusion injury, resulting in increased hemorrhagic transformation during reperfusion(de Court et al., 1989;de Court et al., 1988). Marked blood-brain barrier disruption with formation of brain edema has been found in hyperglycemic rats after temporary and permanent middle cerebral artery occlusion(Kamada et al., 2007). In diabetes adaptive protective mechanisms gradually develop, protecting the subject against acute hyperglycemia. Diabetes promotes neovascularization, remodeling and increases in vascular tone limiting cerebral perfusion(Ergul et al., 2009). Resulting hypoxia and/or metabolic changes mediate ischemic tolerance via neuronal preconditioning but decreases vascular ischemic tolerance leading to increased and accelerated hemorrhagic transformation and development of edema in the event of an ischemic event. Acute hyperglycemia also increases vascular tone and disrupts vascular integrity but in the absence of sufficient time to stimulate adaptive protective mechanisms, the magnitude of neuronal damage is greater.

Cerebral ischemia results in widespread activation of the systemic inflammatory system (Offner et al., 2006). Systemic inflammatory mediators such as cytokines and adhesion molecules can activate microglial cells and perivascular macrophages and contribute to irreversible brain ischemia(Bemeur et al., 2007). After the initial activation of the innate immune response, inflammatory cells from the periphery are mobilized and contribute to microvessel obstruction, edema formation, cellular necrosis and tissue infarction.

Hyperglycemia enhances neutrophil infiltration and increases cytokine expression in several animal models of cerebral ischemia and likely exacerbates the ischemic injury(Bemeur et al., 2005).

4. Glucose control in critically ill patients

4.1 Intensive insulin therapy

A number of randomized controlled trials have been performed on the effects of strict glucose control in critically ill patients. Two single centre trials were performed in Leuven by van den Berghe et al(Van den Berghe et al., 2001;Van den Berghe et al., 2006a), followed by a number of multicentre trials. The first Leuven trial compared maintenance of blood glucose levels between 80 and 110 mg/dl versus 180 and 200 mg/dl in critically ill patients in a surgical ICU(Van den Berghe et al., 2001). In this trial strict glucose control resulted in a 42% reduction in mortality compared with conventional treatment. Septic patients and patients with an ICU stay > 5 days showed the largest reduction in mortality. In the second trial from Leuven performed in medical ICU patients no mortality benefit was demonstrated in the overall intention to treat analysis(Van den Berghe et al., 2006a). A reduction in hospital mortality from 52.5 to 43.0 percent was found in patients treated with intensive insulin therapy who stayed in the ICU for 3 days or more. Among patients treated < 3 days in the ICU, mortality was higher in the insulin group compared to the conventional group. The incidence of hypoglycemia was higher in the intervention group compared to the conventional treatment in both trials. Pooling the two datasets of both Leuven trials revealed that intensive insulin therapy reduced morbidity and mortality in a mixed surgical/medical ICU population, especially when continued for at least 3 days, without causing harm to patients treated for < 3 days(Van den Berghe et al., 2006b). The subgroup of patients with a prior history of diabetes did not appear to benefit. Blood glucose maintained at < 110 mg/dl was more effective that at 110-150 mg/dl, but also carried the highest risk of hypoglycemia.

How strict control of blood glucose reduces morbidity and mortality is unknown, but the mechanism may be related either to a direct effect of normalization of hyperglycemia or to the concomitantly higher insulin levels. *Post hoc* multivariate logistic regression analysis of the study by van den Berghe *et al*. suggests that the lowered blood glucose level rather than the insulin dose is related to the reduction in mortality (Van den Berghe et al., 2003). Apart from glucose lowering, insulin has a number of nonglycemic metabolic effects that may be important in critical illness (reviewed in (Honiden & Inzucchi, 2010)). Insulin can modulate inflammation via the mannose binding lectin pathway, via NF-kB and via modulation of pro- and anti-inflammatory cytokines. It can reduce free fatty acids and reverse the state of dyslipidemia in critical illness, regulate apotosis, prevent endothelial dysfunction and hypercoagulation, decrease neutrophil chemotaxis and leukocyte adhesion and prevent excessive nitric oxide which may help regulate oxidative stress.

A retrospective analysis of the databases of the two Leuven trials assessed the effect of intensive insulin therapy on blood glucose amplitude variation and pattern irregularity in critically ill patients(Meyfroidt et al., 2010). The Leuven intensive insulin therapy strategy increased mean daily delta blood glucose while not affecting standard deviation blood glucose. Increased blood glucose amplitude variation and pattern irregularity were associated with mortality, irrespective of blood glucose level. In contrast, the reduced mortality observed with intensive insulin therapy in the Leuven trials could not be attributed to an effect on blood glucose amplitude variation.

After these landmark studies by Van den Berghe in 2001 and 2006, tight glycemic control was adopted as standard care in a large number of ICUs. However, subsequent randomized controlled multicentre trials were unable to replicate the results of these landmark trials. The Glucontrol study compared strict glucose control (blood glucose concentrations 80-110 mg/dL) to a target glucose between 140-180mg/dL, in an attempt to prevent the adverse effects of severe hyperglycemia, while reducing the risks of hypoglycemia(Preiser et al., 2009). This multicentre study was stopped early due to the high rate of protocol violations. Strict glucose control failed to induce any clinical benefit, but was associated with a higher incidence of hypoglycemia. The VISEP trial was a multicenter, two-by-two factorial trial, that randomly assigned patients with severe sepsis to receive either intensive insulin therapy to maintain euglycemia or conventional insulin therapy and either a low-molecular-weight hydroxyethyl starch or modified Ringer's lactate for fluid resuscitation(Brunkhorst et al., 2008). After the first safety analysis, involving 488 patients intensive insulin therapy was terminated early by the data and safety monitoring board, owing to an increased number of hypoglycemic events (12.1%), as compared with conventional insulin therapy (2.1%). No differences in mortality and morbidity between the intensive and conventional treatments groups were found, but patients in the intensive-therapy group tended to have longer stays in the ICU than did patients in the conventional therapy group. The NICE-SUGAR trial was a large, international, randomized trial comparing intensive glucose control, with a target blood glucose range of 81 to 108 mg/dl to conventional glucose control, with a target < 180 mg/dl(Finfer et al. 2009). Intensive glucose control increased the absolute risk of death at 90 days by 2.6 percentage points; this represents a number needed to harm of 38. The difference in mortality remained significant after adjustment for potential confounders. Severe hypoglycemia was significantly more common with intensive glucose control. Given this lack of reproducible results in a heterogeneous group of ICU patients, and concerns over excessive hypoglycemia, extremely tight glucose control cannot be considered standard of care in ICU patients.

The multicentre trials were unable to replicate the findings of the 2 Leuven trials and raised the possibility that intensive insulin therapy may even increase the risk of mortality and morbidity in ICU patients. The explanation for the disparate findings seems multifactorial. In the Leuven studies the rate of use of total parenteral nutrition was higher compared to the other studies. Intensive insulin therapy may increase mortality in patients receiving enteral nutrition, possibly related to the adverse effects associated with hypoglycemia(Marik & Preiser, 2010). In turn, high dose parenteral glucose administration in the absence of intensive insulin therapy results in hyperglycemia with associated organ failure and death. In the Leuven studies, adjustments of insulin dosage were exclusively based on blood glucose measured on arterial blood via a point-of-care blood gas/glucose analyzer, whereas other studies used samples obtained from different sites and measured with different devices. The conventional treatment differed among the studies(Gunst & Van den Berghe, 2010). In the Leuven studies higher glucose values were tolerated compared to the other trials and the beneficial effects of intensive insulin therapy in these studies may be obtained by preventing excessive hyperglycemia.

4.2 Intensive insulin therapy in brain injury

Hyperglycemia at the time of brain injury is associated with increased morbidity and mortality. A planned subgroup analysis in patients with isolated brain injury of the first

Leuven study revealed that intensive insulin therapy resulted in lower intracranial pressures, less seizures and a better long-term rehabilitation. Strict glucose control also protected general ICU patients against critical illness polyneuropathy.

A number of small studies on glucose control in critically ill neurological patients have been published, but most of these trials were too small to achieve sufficient statistical power to demonstrate possible effects on neurological outcome or mortality. Intensive insulin therapy did not change the incidence of vasospasm, neurological outcome or mortality rates in patients with acute subarachnoid hemorrhage(Bilotta et al., 2007). A decrease in infection rate from 42 to 27% was observed in the patients with strict glucose control compared to conventional glucose control. No differences in neurological outcome or mortality rates were found in patients after severe traumatic brain injury(Bilotta et al., 2008;Coester et al., 2010). A trial in 483 patients undergoing elective or emergency brain surgery revealed that intensive insulin therapy significantly reduced the length of stay in the ICU (6 vs. 8 days), and the infection rate (25.7% vs. 39.3%) without a significant effect on neurological outcome or survival at 6 months(Bilotta et al., 2009). In the UK Glucose Insulin in Stroke Trial (GIST-UK) patients presenting within 24 hours of stroke onset were randomly assigned to receive glucose-potassium-insulin infusion aiming at a capillary glucose between 72-126 mg/dL or no glucose intervention(Gray et al., 2007). The trial was stopped due to slow enrolment after 933 patients were recruited. There was no significant reduction in mortality or neurological disability at 90 days, although the study was underpowered and alternative results could not be excluded. The Treatment of Hyperglycemia in Ischemic Stroke (THIS) trial revealed similar results(Bruno et al., 2008). Strict versus moderate glucose control did not improve outcome in patients after resuscitation from ventricular fibrillation(Oksanen et al., 2007). Intensive or conventional control of blood glucose levels in mechanically ventilated adult neurologic ICU patients resulted in a non-significant increase in mortality in the patients in the intensive insulin group (36 vs 25%), with no differences in functional outcome(Green et al., 2010).

The results from the studies on strict glucose control in unselected critically ill patients may not be directly applicable to patients with critical neurological disease because of the high sensitivity of the brain to the effects of hypoglycemia. Tight glucose control was complicated by an increased number of hypoglycemic events in all trials in critically ill neurological patients. Since studies in patients with acute brain injury did not show a beneficial effect of strict glucose control on mortality or neurological outcome, the markedly increased risk of hypoglycemia limits the safe use of intensive insulin therapy these patients.

5. Glucose monitoring in the ICU setting

Detection of hypoglycemia is difficult in ICU patients since these patients are often sedated and incapable of communicating, thereby masking clinical symptoms and signs. Frequent glucose measurement is therefore required to titrate the amount of insulin and detect episodes of hypoglycemia. For practical reasons bedside point of care (POCT) devices are frequently used. The accuracy of the POCT monitoring is influenced in several ways, including both preanalytic and analytic parameters. Glucose concentrations may differ according to the blood sampling site (venous, arterial or capillary blood). In critically ill patients, capillary blood glucose measured by fingerstick is inaccurate(Critchell et al., 2007;Kanji et al., 2005). Capillary sampling led to both overestimation(Kanji et al., 2005) and underestimation(Atkin et al., 1991) of blood glucose values. The presence of shock, use of vasopressors and upper extremity edema were associated with the occurrence of inaccurate readings.

The reliability of the POCT devices itself in critically ill patients is also poor. In a prospective observational study the performance of 3 different POCT devices was tested and compared with the glucose oxidase method in arterial blood samples(Hoedemaekers et al., 2008). To minimize preanalytical bias the measurements were performed simultaneously by an experienced laboratory technician under controlled circumstances using a single arterial blood sample. Paired samples from all 3 tested devices were inaccurate in 4.9-13.4% of measurements. Inaccurate glucose readings were most frequently falsely elevated, and occurred over the entire range of blood glucose values. Patients with inaccurate POCT glucose results were significantly older, had a higher disease severity score, and a higher ICU mortality compared with patients with accurate glucose values. The mechanism underlying the differences in glucose values between the different POCT systems and the glucose oxidase method in critically ill patients is unknown. Accu-Chek uses the glucosedehydrogenase-pyrroloquinolinequinone method for glucose determination, which is not specific for glucose. This method misinterprets maltose, icodextrine (which is converted to maltose), galactose, and xylose as glucose, leading to erroneously elevated glucose levels (Schleis, 2007). In addition, a large number of drugs commonly used in the treatment of critically ill patients, such as acetaminophen, dopamine, and mannitol, interfere with a number of POCT test systems. Changes in hematocrit concentration can influence the results of POCT measurements. Depending on the point-of-care testing device that is used both overestimation and underestimation of the glucose values can occur in patients with low hematocrit levels(Karon et al., 2008). Glucose measurement in the ICU setting using these bedside devices can be inaccurate and potentially dangerous: inaccurate glucose readings are most frequently falsely elevated, resulting in misinterpretation of high glucose values with subsequent inappropriate insulin administration or masking of true hypoglycemia.

In the past decade continuous glucose measurement devices have been developed in order to make glycemic management safer and more efficient. Due to concerns regarding altered perfusion in critical illness, many have questioned the accuracy of such devices in ICUs. So far, both excellent and poor performance has been reported in ICU patients (Bridges et al,. 2010;Corstjens et al., 2006;Holzinger et al., 2009;Price et al., 2008). Until these matters are solved, continuous monitoring of interstitial glucose values should be used with caution in the ICU.

6. Conclusion

Glucose control in the ICU is markedly different from that in an out-patient clinic. Severe illness induces dysglycemia, with potential detrimental effects of low, high and variable glucose values. The injured brain is particularly susceptible for changes in glucose concentrations. strict glucose control is not proven beneficial in neurological ICU patients and has a unacceptable risk of hypoglycemia. Glucose control in the neurological ICU should be focused on maintenance of a steady level of glucose between 8-10 mmol/l, avoiding large fluctuations. Glucose monitoring in neurological ICU patients is difficult and requires special attention.

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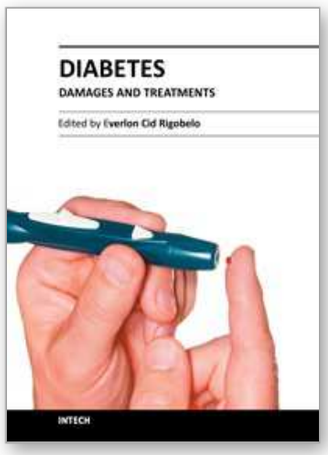
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Over the last few decades the prevalence of diabetes has dramatically grown in most regions of the world. In 2010, 285 million people were diagnosed with diabetes and it is estimated that the number will increase to 438 million in 2030. Hypoglycemia is a disorder where the glucose serum concentration is usually low. The organism usually keeps the serum glucose concentration in a range of 70 to 110 mL/dL of blood. In hypoglycemia the glucose concentration normally remains lower than 50 mL/dL of blood. Hopefully, this book will be of help to many scientists, doctors, pharmacists, chemicals, and other experts in a variety of disciplines, both academic and industrial. In addition to supporting researcher and development, this book should be suitable for teaching.

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