R E V I E W - E M E R G E N C Y   M E D I C I N E

Evaluation and treatment of hyperglycemia in critically ill patients

Andrea Balloni[1], Federico Lari[2], Fabrizio Giostra[1]

[1] Medicina e Chirurgia d'Accettazione e d'Urgenza - Area Vasta 4 Fermo, [2] Medicina della Pianura AUSL, Bologna

Summary. The hyperglycemic reaction to stress is part of adaptive metabolic response to critical illness, especially hypoxia, hemorrhage and sepsis. It involves neuro-endocrine and immune pathways leading to the development of insulin resistance and hepatic glucose production by gluconeogenesis and glycogenolysis. Over the last years the concept of stress related hyperglycemia has been replaced by the concept of dysglycemia and its three domains: hyperglycemia, hypoglycemia and glycemic variability. Each of the three domains is independently associated with increased risk of mortality in patients admitted in intensive care unit and non critically ill patients, both medical and surgical. The strongest association with mortality is demonstrated for hypoglycemia, with additive negative effects for hyperglycemia and glycemic variability. The influence of pre-existing diabetes mellitus on the relation of the three domains of dysglycemia with mortality is not clear, suggesting that patients affected by diabetes mellitus may tolerate a larger glucose variability. Advances in continuous glucose monitoring systems and insulin therapy algorithms may reduce the development of glycemic variability and hypoglycemia, but the benefits in clinical practice have not yet been established in clinical trials. (www.actabiomedica.it)

Key words: stress hyperglycemia, hypoglycemia, glucose variability, continuous glucose monitoring

Introduction

Glycemic control and stress hyperglycemia in critically ill patients reached a particular attention in the last 20 years with a huge increase of clinical studies in medical and surgical departments to identify the best glycemic target and the best insulin algorithm treatment for patients with abnormal glycemic control (1). It is commonly accepted in literature that acute illness may conduce to hyperglycemia, glucose intolerance and insulin resistance. Glycemic deregulation is associated with a poor outcome in critically ill patients with an increase of mortality and morbidity, such as increase of infections, medical and surgical complications and length of hospitalization. This association is the same for first glycemic value at hospital admission and for average glycemic value during hospitalization (2-3). Insulin administration is used to improve clinical outcomes but the role of insulin therapy in critically ill patients is nowadays not clear.

The Leuven Study

In 2001 Van der Berghe et al edited the results of a large prospective randomised controlled trial, non blinded, performed in a single surgical centre in Leuven (Belgium) to examine the effects of tight or conventional glycemic control in critically ill patients (4). The 1548 patients enrolled in the study were admitted in surgical intensive care unit, receiving mechanical ventilation, in prevalence for cardiac surgery. Patients

randomly received intensive insulin therapy with a target between 80 mg/dl and 100 mg/dl of blood glucose or a conventional insulin therapy with a blood glucose target between 180 and 200 mg/dl. Insulin was administrated by continuous endovenous infusion and glycemic control was tested with arterial blood samples. After one year, patients in intensive insulin therapy presented a reduction of mortality compared to patients in conventional insulin therapy (p<0.04) and a reduction of medical complications such as infections, sepsis, acute renal failure, prolonged mechanical ventilation, transfusions and duration of hospitalization. The authors concluded that a strict glucose control reduces mortality and morbidity in surgical critically ill patients. Before the publication of Leuven study, glycemic control among critically ill patients did not receive sufficient attention. These encouraging results changed the way to recognize and to treat hyperglycemia in intensive care units all over the world. As a consequence in the following years the intensive insulin therapy became the new gold standard for the treatment of medical and surgical critically ill patients with impaired glucose control (5).

The positive results in mortality and morbidity emerged in the Leuven study were not replicated in succeeding randomized trials. A series of retrospective and interventional studies suggests prudence for insulin regime with the target of tight glycemic control in medical and surgical critically ill patients (6-7).

The NICE-SUGAR trial

In 2009 Finfer et al edited the results of the NICE-SUGAR trial, the largest multicenter randomized study to investigate glucose control in critically ill patients (8). 6104 medical and surgical patients admitted in intensive care unit were randomly assigned to intensive insulin treatment with blood glucose target between 81 and 108 mg/dl or to conventional insulin treatment with target blood glucose of 180 mg/dl or less. Insulin was delivered by a continuous endovenous way and glucose monitoring was assessed with blood arterial samples. The study showed a higher mortality in patients in intensive insulin therapy than in conventional group (p<0.02) and no difference in morbidity

such as duration of hospitalization or mechanical ventilation, number of severe infections, acute renal failure with renal replacement therapy or multiple organ failure. The group of patients in intensive insulin therapy showed more frequent severe hypoglycemic events (blood glucose <40 mg/dl) than conventional therapy group (p < 0.001).

The NICE-SUGAR trial and other successive studies demonstrated that the adoption of a tight glycemic control in critically ill patients did not lead to any advantages in mortality and morbidity than a moderate insulin treatment. Moreover, the increase in severe hypoglycaemic episodes in patients in intensive insulin therapy may increase morbidity and mortality in this group of patients (9-10).

A possible explanation for the opposite results among randomized trials may lie in the incidence of severe hypoglycemia among patients in intensive insulin therapy. Observational and prospective studies showed a strong independent association between hypoglycemia and mortality (11-12). Moreover glycemic variability, in retrospective and interventional trials, is independently related to mortality.

In literature there were contrastant evidences for the identification of the safer and more effective insulin infusion therapy for an euglycemic target in medical or surgical patients admitted in intensive care unit. In particular the beneficial effects of intensive insulin therapy are evident in surgical intensive care unit (13). A glycemic end point between 150 mg/dl and 180 mg/dl seems to be the most practicable to avoid the onset of adverse events and severe hypoglycemia. It is also necessary to resort to a validated and standardized insulin infusion protocol with repeated arterial glucose samples and adequate nutritional support, and to a monitoring system for insulin protocol to avoid hypoglycemia and to reduce glycemic variability (14).

Pathophysiology of stress hyperglycemia

Critically ill patients, with previous history of diabetes or normoglycemia, commonly present elevated blood glycemic levels. Hemorrhage, hypoxia and sepsis are the stressors that induce the highest release of stress hormones (15). Patients develop stress hypergly-

cemia for esogenous causes such as medical therapies, bed rest and endogenous factors such as inflammatory cytokines and stress hormones produced by the hypothalamic-pituitary-adrenal axis and the sympathoadrenal system (16). Proinflammatory cytokines (TNF-α, IL-1 and IL-6), cortisol, epinephrine and norepinephrine, induce stress hyperglycemia by excessive gluconeogenesis, glycogenolysis and insulin resistance in peripheral tissues such as the skeletal muscles (17). Insulin resistance is also favored by the altered release of adipokines from adipose tissue (18). Medical therapies may induce hyperglycemia, by the administration of exogenous catecholamines and corticosteroids, dextrose infusion, parenteral nutrition. Acute hyperglycemia may induce a poor outcome in critically ill patients by complications common in chronic diabetic patients such as increased risk of infections, worse wound healing, polyneuropathy. Furthermore, acute hyperglycemia may cause injury to endothelial cells, hepatocytes, and renal tubular cells (19-20). However, the elevated glycemic concentrations can be useful in critically ill patients and a permissive hyperglycemia can be considered an adaptive response to acute illness. Hyperglycemia in fact enhances the glucose diffusion gradient in ischemic tissues while insulin resistance promotes the redistribution of glucose in non-insulin-dependent tissues including central and peripheral nervous system, bone marrow, white and red blood cells and reticulo-endothelial system. Moderate hyperglycemia (blood glucose concentrations between 140 and 220 mg/dL) promotes cellular glucose uptake without hyperosmolarity complications (21). In addition, acute permissive hyperglycemia may favour anti-apoptotic and angiogenetic pathways (22-23).

Three domains of glycemic control: hyperglycemia, hypoglycemia and glucose variability

Several studies showed that the degree of hyperglycemia may have a prognostic role and be correlated to the severity of the disease. However, this relationship does not appear a pure cause and effect association. There are recent evidences that hyperglycemia is predictive of mortality in non diabetic patients affected by sepsis only if the blood glucose levels are corrected

for lactatemia (24). Moreover, several studies concluded that the relation between hyperglycemia and in-hospital mortality is stronger among non diabetic patients than in those with pre-existing diabetes mellitus. Nowadays, there is growing evidence that diabetic and non diabetic critically ill patients present a different dysglycemic response (25). Hypoglycemia is associated with mortality in both diabetic and non diabetic patients, but outcomes associated with glycemic variability differ according to premorbid diabetic status. Glycemic variability induces a significant increase of mortality among non-diabetic patients (26). The differences between patients with diabetic and non diabetic pre-existing morbidity open to the possibility that glycemic control protocols and glycemic target for critically-ill patients will differ according to pre-admission glycemic control levels (based on HgbA1c concentrations at the in-hospital admission) and other markers of insulin resistance, such as metabolic syndrome (27).

The emergence of hypoglycemic episodes is a frequent event among patients treated with intensive insulin therapy. Severe hypoglycemia (blood glucose level less than 40 mg/dl) arises in up to 28% of patients with tight glycemic control target in major trials (1). Hypoglycemia is harmful by different mechanisms, such as cardiac arrhythmia, alteration of inflammatory responses, irreversible neuronal damage and autonomic instability (28). The development of continuous glucose monitoring systems and better glycemic control algorithms allowing to a significant reduction in the incidence of hypoglycemic episodes may demonstrate possible advantages of a tight glycemic control strategy in critically ill patients.

Currently, there is not any gold standard accepted for measuring glycemic variability. Glycemic variability may be defined in different ways such as the standard deviation of the arithmetical mean of all blood glucose measurements during intensive care unit stay, or the mean absolute glucose change and the mean amplitude of glycemic excursion. Despite glycemic variability definition, several studies showed that it is an independent predictor of mortality in critically ill patients, causing oxidative stress and inducing cell apoptosis (29-30). It is desirable that the advances in glycemic monitoring and glucose control algorithms will reduce the extent of glycemic variability.

These findings remind that nowadays the role of hyperglycemia in critically ill patients is incomplete understood and, to optimize glycemic control, hyperglycemia, hypoglycemia and glycemic variability must be considered together.

Glucose monitoring systems

Conventional glucose monitoring systems require frequent blood glucose measurements and hypoglycemic episodes may not be observed between two glucose detections (31). The development of continuous glucose monitoring systems may conduce to a successful management of hyperglycemia, reducing hypoglycemic episodes and glycemic variability (32). We can suppose that a continuous measure of intravenous glucose levels in critically ill patients will reduce the incidence of insulin induced hypoglycemia and the fluctuations of glucose levels. The further treatment step may be the direct connection of the continuous sensor to glucose control algorithm in a complete automated closed-loop system (33). In recent years, several small studies investigated the accuracy and the dependability of continuous glucose monitoring systems in critically ill patients, reporting an association with a decreased risk of severe insulin induced hypoglycemic episodes (34). Furthermore, we still do not know whether continuous glucose monitoring systems reduce medical costs and nurses workload and improve prognosis of patients (35-36).

Conclusions

In critically ill patients, hyperglycemia is common ad associated with adverse outcomes. Several studies showed that both hypoglycaemia and severe hyperglycemia increase in-hospital mortality. In particular they draw a J-curve relationship between blood glucose concentration and mortality. The use in real practice of novel technologies such as continuous glucose monitoring systems and computer-based insulin infusion algorithms may help to achieve a good glucose control, avoiding the risk of hypoglycemic episodes.

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Correspondence:
Andrea Balloni
Via Luciano Pavarotti, 3
60027 Osimo (AN)
Fax 0734 6252282
E-mail: andrea.balloni@yahoo.it