On the Management of Hyperglycaemia in Critically Ill Patients Undergoing Surgery

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Abstract

Hyperglycaemia is a major health risk and a negative determinant of surgical outcome. Despite its increasing prevalence, the limited treatments for restoration of normoglycaemia make its effective management a highly complex individualized clinical art. In this context, we review the mechanisms leading to hyperglycaemic damage as the basis for effective management of surgical complications of diabetic and non diabetic critically ill patients.

Keywords: Hyperglycaemia; Surgical complications; Critically ill patients

Evidence of Hyperglycaemic Damage

The development of most adverse outcomes of hyperglycaemia, including increased inflammatory mediators, endothelial cell dysfunction, defects in immune function, haemostatic deregulations leading to thromboses and increased oxidative stress from elevated reactive oxygen species (ROS) and superoxide anion production, has been widely studied \cite{[5, 6]}. Furthermore numerous clinical parameters are also being adversely affected by hyperglycaemia in critically ill patients like duration of stay in the intensive care unit (ICU), duration of ventilatory support and inotropic and vasopressor treatment, number of transfusions, duration of antibiotic therapy, presence of critical illness polyneuropathy, mean APACHE II score and cumulative TISS score and survival \cite{[7]}. In the cardiovascular system, hyperglycaemia contributes to myocyte apoptosis, impaired ischemic preconditioning and increased infarct size \cite{[8]}. Tight control of blood glucose appears to alleviate hyperglycaemic damage and restore islet-graft function by ensuring normal development of new vessels and preservation of endothelial lining in experimental animals \cite{[5, 9, 10]}. Preventing hyperglycaemia-induced dysfunction in cellular systems that allow insulin-independent glucose uptake, like central and peripheral nervous system, endothelial, epithelial and immune cells, would explain some of the protective effects of insulin therapy in critically ill patients \cite{[11]}. In clinical practice, achievement of normoglycaemia before a surgical procedure is carried out, ensures proper activation of the basic steps of the healing process like normal vascul...
larization and inflammatory response [12, 13].

While some experts use routine administration of intensive insulin therapy to normalize glucose levels of hyperglycaemic patients in the ICU, others raise serious concerns over the actual definition of the optimal glucose level, the accuracy of measurements, the resources required to attain tight glycaemic control and the impact of tight glycaemic control across the heterogeneous ICU population including patients with diabetes, previously undiagnosed diabetes or stress-induced hyperglycaemia [14-16].

**Mechanism of Hyperglycaemic Damage**

Mainly hexosamine, advanced glycation end product (AGE) formation and diacylglycerol protein kinase C pathways, activated by increased availability of the glycolytic metabolites glyceraldehydes-3-phosphate and fructose-6-phosphate, are implicated in the pathogenesis of hyperglycaemia induced vascular damage. The lipid-soluble thiamine derivative benfotiamine inhibits the enzyme transketolase, which converts glyceraldehydes-3-phosphate and fructose-6-phosphate into pentose-5-phosphates and other sugars as well as hyperglycaemia-associated NF-kB activation, and might be clinically useful in preventing development and progression of diabetic complications [17].

In critical illness the generation of neuroendocrine responses by acute insults like the stress of surgery and anaesthesia, trauma or sepsis, alters carbohydrate metabolism, causes excessive secretion of counter-regulatory hormones like catecholamines, cortisol, glucagon, and growth hormone, promotes insulin resistance, increases hepatic glucose production via enhanced glycogenolysis and gluconeogenesis and impairs peripheral glucose utilization and insulin action. Four glucose transporters, GLUT-1, GLUT-2, GLUT-3 and GLUT-4, facilitate insulin-independent glucose transport in these tissues. In critical illness, cytokines, VEGF, TGF-β and hypoxia appear to up regulate the expression and membrane localization of GLUT-1 and -3 transporters in different cells types. This “stress response” may overrule the normal protection of cells against hyperglycaemia, thus allowing cellular glucose overload. Hence, all organ systems that take up glucose independent of insulin may be at high risk for direct glucose toxicity by the consistently attained high levels of these regulators during critical illness [18].

Insulin binding to its receptors activates two main branching pathways: a) the mitogenic or “growth signal” and b) the metabolic. The former affects cell proliferation and the latter activates protein kinase B (PKB) leading to nitric oxide (NO) generation and apoptosis via metabolic mobilization of glucose, lipid, and protein stores. In patients with long standing diabetes, the metabolic consequences of insulin resistance are mediated predominantly by abnormalities along the metabolic pathway of insulin signalling caused primarily by exogenous insulin administration. However, a disrupted metabolic pathway does not mean that the mitogenic signalling path will also be equally unresponsive. Compensatory hyperinsulinemia may thus still exert mitogenic actions in certain cell types while the metabolic actions of insulin are suppressed. This discrepancy may occur in vascular smooth muscle cells and in specific capillary endothelial cells of patients with type-2 diabetes and obesity. Whether insulin resistance is similarly “selective” during critical illness and hyperinsulinemia exerts adverse effects through this pathway in the acute setting of severe illness is presently unknown [18].

**Clinical Prevention of Hyperglycaemic Damage**

Clinical evidence suggests that glycaemic control is independent predictor of patient survival and normoglycaemia is beneficial on surgical outcome [19-21]. Achievement of a normoglycaemic environment long before a surgical procedure is carried out ensures proper activation of the basic steps of the healing process like normal vascularization and inflammatory response [6, 13]. One study reported that only 40% of 25 ICU patients achieved target blood glucose levels using accepted insulin infusion, initiation and maintenance algorithms [22], while another including 50 patients reported considerably broader success rates ranging from 25% to over 70% [23]. Recent multi-center trials of intensive glycaemic control in critically ill patients using more (4.4 - 6.1 mmol/L) [24] or less (4-8 mmol/L) [25] stringent glucose targets yielded similar patient mortality rates [25-30].

Recent guidelines for the glycaemic control of ICU patients with severe sepsis recommend the use of validated protocols for insulin dose adjustment to maintain blood glucose < 150 mg/dL (8.3mmol/L) [31, 32] Implementation of analogous insulin infusion algorithms to secure tight insulin control in a broader spectrum of critically ill patients in the ICU however, led to increased rates of hypoglycaemia of unclear clinical significance [33]. The increased variability of circulating glucose during critical illness has negative effect on therapeutic intervention and deleterious impact on survival, particularly of non-diabetic hyperglycaemic patients. Van den Berghe reported the incidence of hypoglycaemia (< 40 mg/dL or 2.2 mmol/L) associated with tight glycaemic control in a medical ICU, as high as 18.7%. Application of various approaches and computer-based algorithms may definitely improve this high incidence. The impact of hypoglycaemia, particularly in patients with septic shock and those with neurological compromise, warrants further evaluation [34-36].

The clinical benefits of intensive insulin therapy for prevention of hyperglycaemia after surgery are yet controversial. One study reported reduced morbidity and death of critically ill patients undergoing primary cardiac surgery [23].
Clearly, glycaemic control of critically ill patients is a highly individualized clinical art that requires coordinated management by health care professionals. Future improvements in the management of these patients are likely to profit from advances in: 1. Targeted prospective clinical research protocols aiming to delineate the systemic effects of hyperglycaemia and insulin therapy and 2. Predictive marker-guided insulin administration protocols able to achieve and maintain glycaemic targets with minimal side effects like hypoglycaemia.

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