



Tight Perioperative Glucose Management Should Start in the Operating Room

CON

Introduction

Perioperative control of blood glucose during cardiac surgery has been shown to decrease the incidence of post-operative infection. It is now widely believed that the benefits of perioperative blood glucose control may be applicable to other surgical procedures also. And it is now being suggested that the blood glucose should be controlled perioperatively in a very “tight range” during all surgical procedures. However, despite this widespread belief of the benefits of tight glycemic control, some very fundamental questions remain unanswered. There is no consensus of the target patient population (Diabetics vs. Non-Diabetics) for whom it may be most beneficial, timing (Preoperative vs. Perioperative), the optimal glucose level and the duration of tight control. Last but not the least, the exact definition of “tight blood glucose control” is also a subject of considerable debate. Should tight glucose control be defined as keeping the glucose at a non-diabetic level (65 to 110mg/dl), or at an impaired glucose tolerance level (140mg/dl), or 140-180mg/dl, or keeping the glucose level <150mg/dl in all patients at all times? The blood glucose level can even be affected by the method of measurement, i.e. the capillary method of measurement of blood glucose with a glucometer overestimates the true blood glucose level when compared to the laboratory measured level (1). Finally, it remains an unresolved issue that whether the beneficial effects of glycemic control are due to the glycemic control or due to the metabolic effects of insulin independent of the blood glucose level(2).

The beneficial effects of glycemic control were brought to attention by van den Berghe et al who demonstrated a decrease in mortality from 8% to 4.6% in the intensive insulin therapy (IIT) group in the surgical intensive care unit (SICU) (3). In IIT group the blood



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sugar was maintained between 80-110mg/dl, while in the control group the blood sugar was maintained between 180-200mg/dl. The authors repeated the study in 2006 in the medical intensive care unit (MICU) patients showing similar results in patients on IIT for at least three days in the MICU (4). In both these studies there was an increased risk of hypoglycemia in the IIT group, in SICU (0.8% to 5.2) and in MICU (3.1% to 18.7%), despite very close monitoring (1:1 nurse-patient ratio). There was actually an INCREASE in mortality in the IIT group patients if their duration of stay in the SICU or MICU was less than three days. Interestingly, there was NO benefit of the IIT in patients with diabetes mellitus. There is evidence that prevention of wide variations in blood glucose level with an insulin infusion may have been responsible for reduction in morbidity and mortality than achieving a specific target glucose level(5). Continuous insulin infusion for IIT is also not an entirely benign intervention. As identified by Rady “Premature and indiscriminate use of intensive insulin therapy may have resulted in preventable deaths across the United States”(6,7). Hypoglycemia under anesthesia may be more severe and may last longer, hence indiscriminate use of IIT in the operating room or in the immediate post recovery phase cannot be advised(8,9). Two large multi-center glucose control trials were stopped prematurely due to a significant risk of severe hypoglycemia and lack of any morbidity or mortality benefit in the IIT group (4,10). It may be more important to avoid hypoglycemia than hyperglycemia because even a single episode of hypoglycemia is associated with increased morbidity and mortality in critically ill patients(9).

Hormonal regulation of glucose

Insulin is not the only hormone involved in the control of blood glucose. It is regulated by a complex interaction of different hormones, paracrine molecules (Bradykinin) and cytokines (Tumor Necrosis Factor) (11). Stress of surgery, anesthesia and severe diseases can result in a temporary insulin deficiency or relative insulin resistance. It seems that hyperglycemia is a nonspecific marker of stress or a side product of a wider physiological derangement and not a specific independent marker of mortality. Also, the apparent benefits of glycemic control in critically ill patients may be due to insulin infusion or a combination of insulin and lower blood glucose. Insulin enhances erythropoiesis, reduces hemolysis and cholestasis. There is also improved anabolic effect of insulin on respiratory muscle function thus improving liberation from mechanical ventilation(11,12). It appears that the key factor in improving the outcome may be the beneficial effects if insulin rather than an arbitrarily selected specific blood glucose level.

Cerebral protection

Chronic hyperglycemia can lead to a 20% reduction in non-carrier diffusion of glucose in the brain tissue(13,14). Hence diabetics with increased plasma glucose can develop cerebral symptoms of hypoglycemia even when plasma glucose is lowered aggressively to normal range(15). The benefits of blood glucose control in acute

cerebral ischemia in improving outcome were achieved when the threshold for blood glucose treatment was kept at 130 mg/dl and not the recommended "tight" range of 80-100 mg/dl (16,17). The adrenergic symptoms of hypoglycemia are difficult to identify in severely ill patients, who are sedated, paralyzed and dependent on mechanical ventilation, and it may be unsafe and more harmful to expose them to any episode of hypoglycemia(9).

Cardiac protection:

The role of long-term blood glucose control to improve outcomes in cardiovascular disease is well established. There are auto-regulatory mechanisms to control glucose metabolism in the myocardium and it adapts to ischemia through intrinsic myocardial response system that is independent of insulin levels in the blood (11). There is recent evidence that a tight perioperative glucose control with IIT during cardiac surgical procedures may actually be associated with more adverse outcomes than the conventional glucose control group(18). Even in the initial study the beneficial effect was seen only AFTER three days of IIT(3,19). It seems that the maximum beneficial effects of insulin are apparent only AFTER the physiological response to tissue injury has settled down(20). It may be inferred that IIT may have a very limited role in the perioperative period due to the nature of the stress response that may over ride the beneficial effects of insulin in regulating blood glucose level. Simply controlling the blood glucose for a few hours with IIT may not confer any specific outcome benefits but is more likely to expose the patient to inadvertent hypoglycemic episodes. The degree of elevation of blood glucose may be directly related to the severity of the stress response and this may explain the association of hyperglycemia with adverse outcome. Diabetes mellitus is a chronic condition and randomized prospective trials have shown that long term control of blood sugar in insulin dependent or insulin independent diabetic patients leads to an improved micro-vascular function(21). Whether insulin has any role in acute ischemia reperfusion for the myocardium or other organ systems is not known. It is important to regulate blood glucose in diabetic patients under all circumstances. True "tight" control should equally avoid hyperglycemia and hypoglycemia. The current evidence is suggestive of the role of insulin in modulating the systemic inflammatory response, but the evidence of the benefits of "tight" perioperative blood glucose control is lacking, and it may increase the risk of perioperative hypoglycemia. Hence it may not be prudent to initiate IIT in the operating room.

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