Perioperative Glucose Control

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There has been increasing interest in recent years in the glycemic control of surgical patients. The seminal paper of Van den Berghe and colleagues, who showed in 2001 that mortality and morbidity in critically ill surgical patients was improved with intensive insulin therapy, has been hugely influential in stimulating research in this area. By 2008 a meta-analysis comparing tight glucose control with usual care in critically ill patients evaluated 29 randomized controlled trials and concluded that there were no beneficial effects of tight control on mortality but this regimen was associated with an increased risk of hypoglycemia. Three large trials published after this meta-analysis also failed to show benefits of intensive insulin therapy in critically ill patients. A recent meta-analysis in 2009 again concluded that tight glucose control did not improve mortality and significantly increased the risk of hypoglycemia. There was some benefit, however, in patients admitted to a surgical critical care unit.

In comparison to the many studies investigating glycemic control in critically ill patients, there is a paucity of studies examining surgical patients with the exception of cardiac surgery. In order to reach recommendations for the glycemic management of surgical patients that are logical, achievable and safe the following key topics will be discussed:

- Pathophysiology of the hyperglycemic response to surgery
- Deleterious effects of hyperglycemia and hypoglycemia
- Clinical studies of glycemic control in surgical patients
- Benefits and risks of glycemic control

Pathophysiology of the Hyperglycemic Response to Surgery

An increase in blood glucose concentration during and after surgery is a well recognised component of the “stress response”. The increase in blood glucose reflects the severity of surgery, for example 10-20 mg/dl (0.6-1.1 mmol/l) in surface surgery and 55-90 mg/dl (3.1-5.0 mmol/l) in major vascular and cardiac surgery. Hepatic glycogenolysis and gluconeogenesis are enhanced by an increase in catabolic hormone secretion (norepinephrine, epinephrine, cortisol and growth hormone) in response to surgical trauma. There is an initial failure of insulin secretion to respond to the glycemic stimulus of surgery that is followed postoperatively by the recovery of secretion but with lack of functional effectiveness – insulin resistance. Thus the perioperative period is characterized by functional insulin insufficiency. The mechanisms responsible for the lack of functional insulin are poorly understood and include the inhibitory effects of volatile anesthetic agents and circulating catecholamines on pancreatic beta cell function and the effects of starvation and circulating cytokines in inducing insulin resistance. The obvious method of overcoming this lack of functional insulin is the administration of exogenous insulin, but preoperative carbohydrate loading has been found to improve insulin resistance after major surgery and the use of an insulin “sensitizer”, such as metformin, may improve insulin resistance.

The physiological responses to surgery are similar to those found in an injured wild animal in which they evolved to aid survival. It is difficult with the current clinical emphasis on maintaining normoglycemia to consider that an increase in blood glucose perioperatively could be beneficial. Furthermore, there is considerable observational evidence to show that hyperglycemia, irrespective of cause, is associated with adverse outcomes in hospitalized patients. Nevertheless an acute increase in circulating glucose perioperatively may be necessary as an obligatory energy source for immune cells, particularly lymphocytes, and also to ensure a concentration gradient of glucose from blood to the injured tissues that are relatively avascular.

Deleterious Effects of Hyperglycemia and Hypoglycemia

Acute hyperglycemia has many harmful effects such as impaired endothelial NO generation with decreased vasodilation, increased expression of endothelial and leucocyte adhesion molecules, reduced complement function, impaired neutrophil function and increased cytokine synthesis. Together these changes enhance the inflammatory response to injury and likelihood of infection. Many of these responses are shown at glucose concentrations of 180-200 mg/dl (10.0-11.1 mmol/l). The use of insulin to reduce hyperglycemia has been shown to decrease endothelial activation, protect hepatic mitochondria, stimulate glucose uptake, improve the circulating lipid profile and decrease circulating inflammatory markers. Pro-inflammatory cytokines are increased by acute hyperglycemia in the absence of injury and can then perpetuate the raised glucose by inducing peripheral insulin resistance. Current evidence suggests that any beneficial effects of insulin treatment result from a decrease in circulating glucose values.
Hypoglycemia is an obvious risk from the use of insulin infusions to control glucose perioperatively. The brain is particularly vulnerable to hypoglycemia, especially the superficial layers of the cortex. The two meta-analyses examining glucose control in critically ill patients reported relative risks of 5.12 and 6.06 respectively for hypoglycemia in the intervention groups. In diabetic patients hospitalized in general wards it has been shown that patients with hypoglycemia have increased duration of stay and greater mortality during and after admission. It is possible that any benefit of glycemic control in the larger group of critically ill patients without hypoglycemia is more than opposed by serious adverse events in the subgroup who develop hypoglycemia.

GLYCEMIC CONTROL IN SURGICAL PATIENTS

Most of the surgical studies have been undertaken on cardiac patients usually with cardiopulmonary bypass. Cardiac surgery is of particular interest following the demonstration of the beneficial effects of a glucose-insulin-potassium infusion in patients with acute myocardial infarction, although this was not confirmed by a later trial and the long established observation of increased infection rates in diabetic patients. Several retrospective studies have shown beneficial effects of intraoperative control of blood glucose with improved mortality, major morbidity, decreased duration of hospital stay and decreased wound infection. Many of these studies had methodological problems and included predominantly diabetic patients. A recent randomized controlled trial compared tight intraoperative glucose control (target glucose 80-100 mg/dl, 4.5-5.6 mmol/l) with conventional treatment (target glucose < 200 mg/dl, 11.1 mmol/l) in patients, non-diabetic and diabetic, undergoing on-pump coronary artery bypass grafting. There was no decrease in perioperative mortality and morbidity. The pros and cons of tight glycemic control in cardiac surgery remain controversial.

Glycemic control after surgery has been shown to decrease the risk of wound infection in diabetic patients. Studies on non-diabetic patients are conspicuously lacking. A retrospective survey of patients undergoing peripheral vascular surgery found that increased circulating glucose values postoperatively were an independent risk factor for infection. The use of intensive insulin therapy after brain surgery to achieve target blood glucose values of 80-110 mg/dl (4.4-6.1 mmol/l) compared with conventional treatment – blood glucose < 215 mg/dl (11.9 mmol/l) decreased the infection rate but was associated with an increased frequency of hypoglycemia.

No prospective study has compared the effects of perioperative glycemic control in diabetic and non-diabetic patients. Subgroup analysis of the many studies on glycemic control in critically ill patients has yielded conflicting conclusions. Early work suggested that although intensive insulin therapy improved outcome in non-diabetic patients, it was of no benefit in diabetic patients. In contrast, a retrospective case-control study found no difference in mortality between diabetics and non-diabetics despite higher glucose values in the former group. It is possible that diabetic patients may tolerate a higher glucose than non-diabetics perioperatively as a result of their chronic hyperglycemia. Intraoperative glucose control in cardiac surgical patients has focused on diabetic patients with many studies showing improved outcomes (see above). A comparison of glycemic control in type 1 and type 2 diabetic patients has not been undertaken. It is likely that type 2 diabetics who already have marked insulin resistance will require more insulin to achieve glycemic control.

BENEFITS AND RISKS

The institution of glycemic control perioperatively has associated costs. It has been argued that such investment will lead to savings from improved clinical outcomes. There have been several reports that glycemic control programs have resulted in savings attributable to fewer complications, decrease in stay in ICU and hospital and lower laboratory costs. However, these studies relate to critically ill patients and cardiac surgical patients, particularly diabetics.

The risk of hypoglycemia is the major problem in trying to establish tight glycemic control (< 110 mg/dl, < 6.1 mmol/l) and has been found to occur commonly. Patients particularly at risk of hypoglycemia include the elderly, the malnourished and those with autonomic, renal, hepatic and cardiac failure. Hypoglycemia may also occur from the failure to monitor blood glucose frequently and from insulin dosage errors. The long term effects of hypoglycemia in surgical patients are unknown. In diabetic patients recurrent episodes of hypoglycemia have been shown to result in neuronal deficits, especially in children and the elderly.

Safe glycemic management is dependent totally on the frequent and accurate determination of blood glucose concentrations. The US Food and Drug Administration permits a ± 20% error for glucose meters, an inaccuracy that is a major handicap to glycemic control. Glucose values differ between whole blood and plasma although the terms are often used interchangeably. Most commercial glucose meters have a correction factor and report a plasma adjusted value. The assay strips used with glucose meters and arterial blood gas analysis tend to overestimate glucose values at low concentrations with the risk of missing hypoglycemia. Other factors that affect blood glucose measurements include peripheral hypoperfusion, anemia, increased circulating bilirubin and uric acid, mannitol, dopamine, dextrin and paracetamol.

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There is debate about the best index of glycemic control perioperatively. It has been suggested that variability in circulating glucose may be more important than the absolute value. Indices of glycemic control include the admission glucose, maximum daily glucose, mean morning glucose, mean overall glucose or a hyperglycemic index. A recent study found that the simple measure of mean daily blood glucose was as informative as more complex metrics.

CONCLUSIONS

The initial enthusiasm for glycemic control during and after surgery has waned after the failure to replicate the findings of Van den Berghe and colleagues in critically ill patients. There is some evidence to suggest that glycemic control in cardiac surgical patients improves mortality, morbidity and infection rates, particularly in diabetic patients. There are no studies in general surgical patients to indicate whether blood glucose control improves outcome. Tight glucose control (bl. glucose < 110 mg/dl, 6.1 mmol/l) is associated with a large increase in the risk of hypoglycemia and cannot be supported. The Consensus Statement of the American Association of Clinical Endocrinologists and American Diabetes Association recommends that in critically ill patients blood glucose should be in the range of 140-180 mg/dl (7.8-10.0 mmol/l) and in non-critically ill patients should be less than 180 mg/dl (10.0 mmol/l). These limits apply to non-diabetic and diabetic patients. The inclusion of glucose targets as an indicator of quality of care is premature and should be reviewed.

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