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Revista Mexicana de Anestesiología

CONFERENCIAS MAGISTRALES
Vol. 34. Supl. 1 Abril-Junio 2011
pp S305-S310

Perioperative management of the diabetic patient

Daniel R. Brown, MD*

*Rochester, Minnesota

The term diabetes mellitus describes several syndromes of abnormal carbohydrate metabolism that are characterized by hyperglycemia. It is associated with a relative or an absolute impairment of insulin secretion, along with varying degrees of peripheral resistance to the metabolic effects of insulin. Diabetes is the most common endocrinopathy, occurring in nearly 10% of the general United States population and roughly one third of patients undergoing cardiac surgery. Given the increasing frequency of obesity, the number of diabetic patients has been projected to double in the next twenty years. Data showing an association between glycemic control and outcomes in hospitalized patients would suggest that glycometabolic regulation may have a profound impact on perioperative outcome. This review will discuss current classification and treatment of diabetes mellitus, the anesthetic implications of diabetes, as well as the available literature addressing glycemic control and outcomes in a variety of patient populations with recommendations for perioperative glycemic management.

CLASSIFICATION OF DIABETES

Currently, diabetes is classified as type 1 and type 2 in an attempt to group by etiology rather than age of onset or type of treatment[1]. Type 1 diabetes is characterized by destruction of pancreatic β cells, leading to absolute insulin deficiency. This destruction is primarily autoimmune mediated though there is a segment of type 1 patients that have no identifiable antibodies and are therefore considered idiopathic type 1 diabetics. Adults with newly diagnosed diabetes may have circulating islet cell antibodies and therefore would be considered to have adult-onset type 1 diabetes. Patients with type 1 diabetes have an absolute requirement for insulin therapy and will develop diabetic ketoacidosis (see below) if not given insulin. Type 2 diabetes accounts for approximately 90% of all diabetic patients and is characterized by variable degrees of insulin deficiency and resistance. There is no diagnostic test that is specific for type 2 diabetes. Although ketoacidosis is not a typical feature of type 2 diabetes, some patients with type 2 diabetes develop diabetic ketoacidosis under certain circumstances (severe infection or other illness). Subtypes of type 2 diabetes are described and include drug and chemical induced (particularly corticosteroids) and gestational (the most common medical problem in pregnancy).

DIAGNOSIS

Currently, the American Diabetes Association (ADA) defines diabetes mellitus as a fasting (8 hours) plasma glucose value > 126 mg/dL (7.0 mmol/L), symptoms of diabetes (polydipsia, polyuria, unexplained weight loss) with a random plasma glucose value > 200 mg/dL (11.1 mmol/L) or a 2-hr post oral glucose challenge (75 g equivalent anhydrous glucose dissolved in water) glucose value > 200 mg/dL (11.1 mmol/L) [2]. The normal value for fasting plasma glucose is < 100 mg/dL (5.6 mmol/L). The ADA defines fasting plasma glucose between 100-125 mg/dL (5.6-6.9 mmol/L) as 'impaired'. Current thinking suggests that abnormalities in insulin secretion and/or action lie along a continuum and that patients with impaired fasting glucose levels are at high likelihood to progress to meeting the diagnostic criteria for diabetes. Recent data support the common clinical observation that patients with increased fasting glucose levels and body mass indexes are at greater risk for hyperglycemia during times of stress such as the perioperative period.

OUTPATIENT TREATMENT

A causal association between glycemic control and the development and progression of microvascular complications (retinopathy, nephropathy, and neuropathy) has been suggested from studies in both type 1 and type 2 diabetic

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patients[3,4]. The effect of improved glycemic control and macrovascular (peripheral vascular and cardiac) complications is less clear. As stated above, glucose management in type 1 diabetic patients relies on supplementation of insulin. Medical therapy of type 2 diabetes often begins with diet modification and exercise and oral pharmacotherapy with a sulfonylurea or metformin. If goal glycemic control is not achieved, alternatives frequently include combined therapy with other oral agents or the addition of insulin. Types and selected properties of various treatment options for glycemic control are listed below.

Common Oral Preparations[5] (short acting agents typically held the day of surgery, longer acting agents up to 2-3 days prior to surgery; Note: for procedures not expected to be associated with a significant interruption of caloric intake, many recommend no change to oral diabetic pharmacotherapy)

Sulfonylureas (First generation: tolbutamide, acetohexamide, tolazamide, chlorpropamide; Second generation: glyburide, glipizide, glimepiride). Increased release of endogenous insulin and enhanced insulin receptor function by binding to ATP-dependent K^+ channels in pancreatic β cells; Variable duration of action, typically less than 24 hours but chlorpropamide up to 72 hours.

Biguanides (metformin). Mechanism not completely understood but decreases hepatic glucose output and increases insulin action; Avoided in patients with renal or hepatic compromise due to association with development of lactic acidosis.

Thiazolidinediones (rosiglitazone, pioglitazone). Increased peripheral glucose uptake and decreased gluconeogenesis via unclear mechanisms.

Meglitinides (repaglinide, nateglinide). Stimulates insulin secretion by binding to ATP-dependent K^+ channels in pancreatic β cells.

Alpha-glucosidase inhibitors (acarbose, miglitol). Decreases GI digestion and absorption of saccharides and thereby glucose synthesis (no need to hold preoperatively).

Common Insulin Preparations[6] (subcutaneous administration, large variation within and between patients)

Short acting	Onset	Peak	Duration
Regular	30-60 min	2-3 h	8-10 h
Lispro/Aspart	5-15 min	30-90 min	4-6 hr
Intermediate acting			
NPH/Lente	2-4 h	4-10 h	12-20 h
Glargine	2-4 h	none	20-24 h
Long acting			
Ultralente	6-10 h	10-16 h	24-48 h

Various strategies for diabetic drug management have been described for fasting preoperative patients. No single method has been shown to be superior. In general, the magnitude and type of drug therapy, anticipated duration of reduced caloric intake and magnitude of procedural-related stress need to be weighed when determining patient-specific recommendations. In patients managed with short or intermediate acting insulin, a common recommendation is to reduce the morning dose of insulin by one half. Implanted insulin pumps may be discontinued or placed on a constant infusion immediately preoperatively. The most important aspect of preoperative management of glycemic control is to determine plasma glucose immediately preoperatively with subsequent insulin or dextrose therapy guided by this result.

END-ORGAN DYSFUNCTION IN DIABETIC PATIENTS

Diabetes is a progressive disease that affects many end organs thus coexisting pathologies must be identified and managed appropriately during the perioperative period for optimal patient outcomes. Unfortunately, up to one third of surgical patients that are diabetic have yet to be diagnosed. Therefore, an elevated glucose determination in a patient not diagnosed with diabetes should prompt the clinician to re-evaluate the patient in terms of risk and anesthetic plan. Major concerns should include:

Cardiovascular disease. While many metabolic diseases accompany cardiovascular disease, diabetes is the most common. Diabetics are at increased risk for cardiovascular disease including hypertension, coronary artery disease, diastolic dysfunction, congestive heart failure, peripheral vascular disease and cerebrovascular disease. Patients may have clinically «silent» myocardial ischemia or infarction. Current American College of Cardiology/American Heart Association guidelines for perioperative cardiovascular evaluation list diabetes, along with a history of ischemic heart disease, compensated or prior heart failure, cerebrovascular disease and renal insufficiency as clinical risk factors to be considered when determining which patients are candidates for preoperative cardiac testing[7]. One area of debate in earlier literature involved the use of β-adrenergic blockade in diabetic patients. The concern from a pathophysiologic standpoint is that β-adrenergic antagonists could worsen glucose intolerance; however, multiple reports have shown no increase in hypoglycemic episodes in diabetic patients receiving such therapy. Furthermore, available data suggest that diabetic patients have increased cardiovascular benefits compared to nondiabetic patients receiving β-blockers. It should be stressed that diabetes is not a contraindication to b-adrenergic blocker administration when such therapy is indicated.

Renal disease. Renal dysfunction commonly develops in diabetic patients and is the leading cause of renal failure

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requiring renal replacement therapy. Angiotensin converting enzyme inhibitors have been shown to decrease albuminuria and progression of renal dysfunction in diabetic patients and are commonly prescribed. Clinicians need to consider renal function when selecting medications (avoiding potential nephrotoxic drugs) and dosing renally cleared drugs.

Other. Peripheral and autonomic neuropathies are common in diabetic patients. Pre-existing neurologic deficits should be noted prior to procedures. Extra care should be taken when positioning diabetic patients as they may not notice pressure points due to neuropathy and may be at increased risk for ischemia due to vascular compromise. Autonomic neuropathy may blunt the compensatory cardiovascular response to hypotension thus predisposing to hemodynamic lability. Autonomic neuropathy may also cause gastroparesis and predispose diabetic patients to pulmonary aspiration. In patients with chronic hyperglycemia, non-enzymatic glycosylation of proteins and abnormal collagen cross-linking may result in decreased joint mobility. Decreased mobility in the temporomandibular and cervical spine joints may contribute to challenging airway management. Finally, as obesity and type 2 diabetes often coexist, the myriad of anesthetic implications related to obesity must also be evaluated and managed.

ACUTE GLYCEMIC COMPLICATIONS

Hyperglycemia with metabolic alterations and hypoglycemia are serious medical conditions that may have devastating sequelae. Hyperglycemia may be associated with diabetic ketoacidosis (DKA) and a non-ketotic hyperosmolar state (NKHS)[8]. In addition, surgical stress may alter glycometabolic regulation, contributing to disruption of glucose homeostasis. The response to glucose metabolism during stress and surgery is difficult to predict but, in general, the perioperative period is associated with relative insulin hyposecretion and increased resistance. Frequently, factors that precipitate these severe alterations in glucose regulation necessitate surgical intervention therefore it is important that perioperative care providers understand the pathophysiology and treatment of these disorders.

DKA. DKA is a life-threatening complication (reported mortality 5-10%) seen predominantly in type 1 diabetic patients that results from insulin deficiency and is characterized by hyperglycemia, dehydration, hyperosmolarity and an increased anion gap secondary to production of ketones. A precipitating event such as infection, surgical stress, trauma or lack of insulin therapy may be identified. Ketone production frequently results in hyperventilation with large tidal volumes (Kussmaul breathing), «fruity» breath and nausea and vomiting. Management is focused on identifying and treating precipitating factors, fluid resuscitation, glycometabolic control and electrolyte replacement. Fluid deficits are frequently large (> 5 liters) and multifactorial including osmotic diuresis, lack of oral intake, emesis and insensible losses from sweating and hyperventilation. Dehydration may result in hypotension and pre-renal stress on an already compromised renal system. Hyperkalemia is frequently present as a result of acidemia-related extracellular potassium shifts as well as tissue catabolism. With treatment, potassium levels often plummet and aggressive repletion should be anticipated. Careful monitoring of renal function and urine output must be maintained as overhydration and potassium supplementation may lead to further patient compromise in the setting of concomitant renal failure. While a sodium deficit is frequently present, the measured sodium may be falsely low due to hyperglycemia and hypertriglyceridemia. Corrected sodium concentrations in the hyperglycemic patient may be estimated by adding 1.5-2.0 mEq/L to the measured sodium value per 100 mg/dL glucose over 100 mg/dL. Other electrolytes, especially phosphorus and magnesium, are often depleted and should be frequently determined, and repleted as indicated, during resuscitation. Intravenous insulin as an infusion should be administered with frequent determination of plasma glucose levels to guide therapy. Intravenous insulin has a rapid onset (minutes) and duration < 1 hour. Treatment with intravenous insulin is an established practice; however intravenous administration of regular insulin in the United States is an «off label» use as this mode of delivery is not currently FDA approved. A dextrose infusion should be started as plasma glucose approaches 200 mg/dL to avoid potential overcorrection of hyperglycemia. Intravenous insulin should be continued until serum ketones are cleared and the acidemia resolved. Patients are at risk for cerebral edema, and subsequent intracranial hypertension, during treatment. Careful monitoring of neurologic status is warranted. Bicarbonate administration is not routine due to concerns of worsening intracellular acidosis, leftward shift of the oxyhemoglobin dissociation curve and increased hyperosmolarity.

Guidelines for DKA management

- Routine monitors plus arterial access (for hemodynamic monitoring and frequent blood sampling) and central venous access (for fluid and electrolyte replacement)
- Aggressive crystalloid replacement (1-3 L in the first hour) starting with 0.9% saline and adjusting free water content of subsequent fluids based on plasma sodium determinations, with subsequent volume replacement individualized to patient response
- Intravenous regular insulin infusion titrated by serial plasma glucose determinations adding a dextrose infusion as glucose values approach 200 mg/dL
- Supplementation of potassium, phosphorus and magnesium as guided by serial plasma determinations

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NKHS. Non-ketotic hyperosmolar states occur predominantly in type 2 diabetic patients during periods of stress such as infection or other illness. Compared to patients with DKA, NKHS patients are typically more dehydrated, hyperosmolar and hyperglycemic. Neurologic alterations are usually present and may include confusion, coma, seizures and/or focal neurological deficits. While patients with NKHS lack the acidemia due to ketone production, severe dehydration may result in significant hypotension leading to lactic acidosis. Thrombotic events may occur due to hypovolemia, hyperviscosity and hypotension. Fluid resuscitation is the mainstay of treatment. Again, 0.9% saline is a reasonable choice for initial resuscitation with the subsequent free water composition of fluid guided by serial sodium determinations. Due to the greater hyperglycemia and hyperosmolarity seen in NKHS patients, they may be at increased risk for developing cerebral edema. More gradual (> 24 hours) correction of hyperglycemia and hyperosmolarity is recommended along with frequent neurologic evaluations.

Hypoglycemia. Hypoglycemia is commonly defined in adults as a plasma glucose < 50 mg/dL (2.8 mmol/L). Altered mental status, progressing to coma and death, along with the physiologic responses to increased catecholamines are the two major ways by which hypoglycemia is most commonly detected. In the perioperative environment, and to a greater extent in the setting of general anesthesia, the ability to recognize these signs and symptoms may be compromised. Clinicians need to have a high index of suspicion for hypoglycemia and frequent determination of plasma glucose levels should be integral to the care of diabetic patients. Hypoglycemia may develop due to residual effects of long-acting insulins, overaggressive antidiabetic treatment or decreased caloric intake. Treatment consists of dextrose administration and correction of the precipitating cause. Since the response to dextrose administration is quite variable, following an initial bolus (25-50 mL of 50% dextrose in adults), serial glucose determinations should be performed and a dextrose infusion considered based on the patient's response.

GLYCEMIC CONTROL IN THE CRITICALLY ILL AND DURING THE PERIOPERATIVE PERIOD

Glycemic control in the critically ill patient is a current topic of debate among anesthesiologists, intensivists and endocrinologists. Available data support an association between hyperglycemia and increased morbidity and mortality in many different surgical and medical populations. A retrospective review of adult medical and surgical inpatients reported worse outcomes in hyperglycemic patients[9]. Hyperglycemia was a common finding, present in 38% of patients, and was associated with an 18-fold increase in in-hospital mortality, a longer length of stay, more subsequent nursing home care and a greater risk of infection. Hyperglycemia in specific disease states has also been shown to be a marker of poor outcomes. A systematic review of 26 studies in adult stroke patients concluded that hyperglycemia is associated with increased mortality and greater risk of poor functional recovery in survivors[10]. The same investigators reached similar conclusions when reviewing the association between hyperglycemia and outcomes in patients with myocardial infarctions[11]. Hyperglycemia with myocardial infarction was associated with increased risk of congestive heart failure and cardiogenic shock in patients without diabetes and in-hospital mortality in patients with and without diabetes.

Retrospective studies linking hyperglycemia and poor outcomes prompted prospective studies investigating whether aggressive management of hyperglycemia could improve outcomes in patients with acute illness. The DIGAMI study followed diabetic patients admitted with acute myocardial infarction and randomly assigned patients to intensive insulin therapy with intravenous insulin compared to routine antidiabetic therapy[12]. Intensive insulin therapy was shown to be associated with significantly reduced long-term mortality (determined at over 3 years average length of follow-up). This demonstration that glycemic control could improve long-term patient survival encouraged investigation in other patient populations. A prospective, randomized trial in critically ill adult patients comparing intensive intravenous insulin therapy with conventional therapy was conducted by Van den Berghe and colleagues[13]. In this trial, patients were randomized to intensive insulin therapy (goal glucose 80-110 mg/dL) or conventional therapy (treat for glucose > 215 mg/dL, maintain 180-200 mg/dL). The trial was stopped early due to a significant reduction in ICU mortality in the intensive insulin therapy group ($p < 0.04$). In addition to decreased ICU mortality, significant reductions in in-hospital mortality and bloodstream infections were also observed. It is notable that in this study, the vast majority of the patients were post-surgical with more than 60% admitted following cardiac surgery. Other investigators have suggested favorable outcomes in post-cardiac surgery patients with improved glycemic control. A report of over 3,500 diabetic patients undergoing coronary artery bypass grafting showed improved glycemic control and an absolute and risk-adjusted decrease in mortality of 57% and 50%, respectively, and decreased infectious complications, following institution of an intravenous insulin management strategy[14].

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In an effort to address whether findings shown in populations with a preponderance of cardiac disease and surgery were more broadly applicable, Krinsley reported retrospective data in an adult ICU with a mixed medical and surgical population showing an association between hyperglycemia and mortality[15]. A subsequent study by the same author reported the effect of instituting an intensive glucose management protocol

in critically ill patients in the same ICU[16]. Institution of the protocol significantly improved glycemic control and was associated with decreased mortality, organ dysfunction, and length of stay in the ICU. As a follow-up to their earlier study in primarily surgical patients, Van Den Berghe and colleagues conducted a prospective, randomized trial similar in design to their earlier trial[13] but in critically ill medical patients[17]. In this trial, mortality was not reduced in the intention-to-treat analysis though morbidity was significantly reduced. Mortality was actually increased in those patients with ICU length of stay less than three days but decreased in those with an ICU length of stay ≥ 3 days. These same investigators performed an analysis of pooled data set from their two randomized controlled trials[18]. Intensive insulin therapy was associated with reduced mortality and morbidity in the intention-to-treat group and in those whose ICU stay was ≥ 3 days.

More recently, several studies have questioned the benefit of the target glucose values in strict glycemic control studies. The GLUCONTROL trial randomized a mixed medical/surgical population to maintain blood glucose between 80-110 and 140-180 mg/dL[19]. The trial was stopped after enrollment of 1,100 patients secondary to the incidence of hypoglycemia in the intensive treatment group. The VISEP trial compared fluid resuscitation and glycemic control using a two-by-two factorial design in septic patients[20]. There was no difference in mortality though the rate of severe hypoglycemia (blood glucose < 40 mg/dL) was significantly higher in the intensive insulin treatment group (17.0 *vs* 4.1%). To date, the NICE-SUGAR study provides the best data comparing target ranges for glycemic control in critically ill patients[21]. This large, international trial investigated 6,104 patients randomized to achieve target glucoses of either 81-108 or less than 180 mg/dL. The groups had similar characteristics at baseline. Mortality was significantly greater in the intensive insulin treatment group (27.5 *vs* 24.9%). The treatment effect did not differ significantly between surgical and medical patients nor were any differences in reported morbidity observed. However, there was a significant increase in severe hypoglycemia observed in the intensive treatment group (6.8 *vs* 0.5%).

There is a growing body of literature which includes intraoperative glycemic control in the study design. A retrospective study of over 6,000 cardiac surgery patients reported high peak serum glucose during cardiopulmonary bypass to be an independent risk factor for death and morbidity in diabetic, as well as nondiabetic, patients[22]. Other investigators have reported perioperative, including intraoperative, hyperglycemia to be a predictor of adverse patient outcomes in cardiac surgery[23,24], carotid endarterectomy[25], and infrainguinal arterial bypass patients[26]. A before-after perioperative, including intraoperative, glucose control protocol study in diabetic cardiac surgery patients reported a significant reduction in mortality, especially in moderate and high risk patients[27].

To date, there are limited prospective data comparing outcomes in patients receiving intensive intraoperative insulin therapy to conventional intraoperative glucose management. Gandhi and colleagues prospectively randomized 400 cardiac surgery patients to receive intensive or conventional glycemic management intraoperatively followed by intensive postoperative glycemic management[28]. While they were able to achieve a significant difference in mean intraoperative glucose concentrations, they reported no difference in a composite 30-day endpoint of death or major morbidity. Interestingly, there were more deaths and strokes in the intensive intraoperative treatment group.

Protocols. It is likely that perioperative practitioners will be asked to obtain tighter glycemic control in their patients (see below). This is currently best accomplished by intravenous insulin administration. Such care is presently part of most critical care practices and various protocols for delivery of intravenous insulin in this setting have been published[13,14,16]. An intraoperative insulin protocol has been validated in cardiac surgery patients[28]. It is important to recognize that protocols rely on frequent determinations of plasma glucose to allow for titration of insulin administration. In addition, since the response to insulin varies from patient to patient and within a patient over time, protocols should allow for variable insulin administration for a given glucose determination (changing the 'sliding scale'). A protocol for treatment of hypoglycemia should also be incorporated into any algorithms for insulin administration.

Unanswered questions. If tighter glycemic control is desired, what glucose level should be targeted? Should severe intensive glycemic control be attempted in all patients? Pathophysiologic reasoning would suggest that avoiding hyperglycemia would be beneficial though this must be weighed against the risks of hypoglycemia. An international multidisciplinary consensus conference was held in 2001 and a position statement on inpatient diabetes and metabolic control developed.[29] In addition to critically ill patients, the consensus statement recommended intravenous insulin therapy during the perioperative period and labor and delivery. The following guidelines were proposed as upper limits for glycemic targets: ICU patients < 110 mg/dL; Non-ICU patients < 110 mg/dL preprandial, < 180 mg/dL maximum; Labor and Delivery patients < 100 mg/dL. However, data published following these recommendations, particularly the NICE-SUGAR study, have questioned the low recommended targets. While certain subpopulations may benefit from stricter glycemic control, it would seem reasonable to avoid perioperative glucose values over 180 mg/dL by using protocols that minimize hypoglycemia. It is advisable that practitioners validate performance of glucose protocols in their own institutions as there are significant differences in measured glucose depending on the glucose monitoring device and technique used[30]. Blood

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glucose variability, not just mean glucose, also appears to affect morbidity and mortality. In a large cohort of over 7,000 critically ill patients, both mean and standard deviation of blood glucose were shown to be independent predictors of ICU and hospital mortality[31]. The optimal balance between target blood glucose and glucose variability is unknown. Other questions remain. Achieving glycemic control is associated with increased resources in terms of time, testing and treatment. How should this be funded? For non-diabetic patients found to be hyperglycemic during the perioperative period, how will we ensure that this information is communicated to primary care providers such that appropriate diabetic testing can occur and, if indicated, treatment initiated?

Policy implications. Despite many questions remaining unanswered, several regulatory and patient advocacy organizations have listed glycemic control as a marker of quality of care. One prominent example calls for cardiac surgery patients to have morning blood glucose values on postoperative days 1 and 2 ≤ 200 mg/dL[32]. The appropriateness of the measurement itself, target level and timing of measurement are debatable.

SUMMARY

Diabetes is the most commonly encountered endocrinopathy and is associated with many end-organ sequelae that impact anesthesia. Acute derangements in glycemic control may be present in patients during the perioperative period and clinicians need to be aware of the pathophysiology and therapy required for optimal patient care. Emerging data link poor outcomes with extremes in perioperative glucose values. Available data would favor maintaining blood glucose values below 180 mg/dL during the perioperative period while reducing blood glucose variability and avoiding hypoglycemia.

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