Thinking Like a Pancreas: Perioperative Glycemic Control

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Perioperative glycemic control is related to patient outcome. Although guidelines for glucose management in hospitalized patients have undergone dramatic changes over the last 5 years, most hospital-based physicians, including anesthesiologists, have not changed their approach to glucose management (1). In this editorial, we discuss the article by Duncan et al. (2) appearing in this issue of *Anesthesia & Analgesia*, review recent recommendations for perioperative glucose management, and highlight areas of uncertainty. We endeavor to improve perioperative glucose management for patients.

There is considerable uncertainty regarding how to manage surgical patients who are taking metformin, an oral hypoglycemic drug. The potential for postoperative lactic acidosis in patients taking this drug has prompted some clinicians and health care systems to routinely cancel surgical procedures if metformin is taken within 48 h of surgery. Other clinicians or health care systems continue metformin, both before and after the surgical procedure. Duncan et al. (2) conducted a retrospective review of a large cohort of diabetic patients admitted for cardiac surgery at their institution who recently took an oral hypoglycemic drug. They compared outcomes among patients who took metformin versus patients taking a non-metformin oral hypoglycemic drug. The authors found that patients taking metformin had lower risks for several complications, and concluded that metformin appeared to be safe for use in the perioperative period.

The article raises several points worthy of reflection. First, the authors used a propensity score to try to account for differences among patients who were taking, versus not taking, metformin. This statistical method used logistic regression, in which metformin becomes the dependent variable. Predictor variables are included in the model (in this case 54 variables) to identify those patient characteristics associated with metformin treatment. The output of this analysis includes a C statistic that is interpreted to mean that, for any given pair of patients, in which one patient received metformin and one did not, how often did the model identify the one receiving metformin? In this analysis, the C statistic was 0.68, suggesting that more than 3 of 10 patients were not correctly classified. Thus, there is the potential that unmeasured differences between groups, and not metformin treatment or nontreatment, could influence the results. Other evidence suggests that propensity scores are no better than standard regressions at controlling for selection bias (3).

Second, the authors evaluated a variety of outcomes, though many were uncommon and did not include explicit definitions, and concluded that metformin was safe. It would be helpful to consider the precise safety of these estimates (3). For example, even if none of the 523 metformin patients had an adverse event in this study, the upper limit of that confidence interval is seven events in 1000 patients. This rate would likely warrant concern from clinicians and lead to alterations of their practice. Rather than thinking of drug safety as a dichotomous variable, (i.e., safe versus unsafe) it may be helpful to think of safety as a continuous variable to help regulators, clinicians, and consumers make a more informed risk/benefit assessment.

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Third, and perhaps most concerning, 70% of patients had poor perioperative glycemic control, defined as four consecutive blood glucose levels >200 mg/dL. Granted, the study enrolled patients from 1994 through 2004, and the evidence to support tight glucose control emerged in the latter years of the study. Nevertheless, it seems that this finding is worthy of further reflection. The evidence regarding the management of glucose in perioperative patients has advanced considerably over the last few years.

PHYSIOLOGY OF INSULIN SECRETION

Below we briefly review the physiology of glucose control with insulin and discuss guidelines for perioperative glucose control put forth by the American College of Endocrinology and supported by the American Society of Anesthesiologists (4). The goals of insulin therapy should be to mimic the physiologic activity of the pancreas, which continuously secretes insulin at a mean rate of approximately 1 U/h in response to hepatic gluconeogenesis. Even when patients are not eating, insulin is continuously secreted. In response to a carbohydrate load, though, a normal functioning pancreas will increase the amount of insulin secreted to maintain a serum glucose of approximately 100 mg/dL. If a patient's blood glucose increases, the pancreas secretes a corrective dose of insulin. Thus insulin secretion by the pancreas can be thought of in three phases: basal, postprandial, and correction.

In trying to mimic this physicality, when using insulin to control glucose in the perioperative period, we need to "think like a pancreas" and replicate the basal, postprandial, and correction phases. All patients, even those who are not eating, require basal insulin. The pancreas normally supplies insulin, and insulin-deficient patients must be given exogenous insulin, either as a continuous IV infusion or as long-acting insulin. Insulin-deficient patients include those with type 1 diabetes who have a history of pancreatectomy or pancreatic dysfunction, wide fluctuations in blood glucose levels, prior diabetic ketoacidosis, insulin use for >5 yr, and/or diabetes for >10 yr. The traditional use of a "sliding scale insulin" regimen does not provide basal insulin. If diabetic patients are eating, clinicians should provide postprandial insulin, generally in the form of short-acting insulin. Finally, sliding scale insulin can be used to correct residual hyperglycemia, though the basal or postprandial dose should subsequently be adjusted to provide better glycemic control (5,6).

There is increasing documentation of the benefits of glycemic control, including decreased rates of surgical site wound infections, and decreased mortality, especially in the perioperative setting (7–10). Given that surgical stress responses increase blood glucose, aggressive glucose control in perioperative patients should be an important priority. The goals of glycemic control in hospitalized patients are well established. The American College of Endocrinology, in conjunction with the American Society of Anesthesiologists, published a position statement that outlines these goals (4) A summary of these guidelines include the following:

1. *Always maintain blood glucose below 180 mg/dL.* There is biochemical evidence suggesting favorable alterations in myocardial and skeletal muscle metabolism, immune function, inflammation, and endothelial cell and platelet function with normoglycemia (4–6).
2. *Maintain blood glucose between 80–110 mg/dL in intensive care unit (ICU) patients.* Van den Berghe et al. (9) demonstrated a reduction in mortality in surgical ICU patients with a >5 day ICU stay with intensive insulin therapy, in which goal glucoses of <110 mg/dL were maintained regardless of their diabetes history (8).
3. *Avoid oral hypoglycemic drugs unless patients are on a regular diet.* Oral hypoglycemic drugs do not maintain tight glycemic control. Although there are no randomized controlled trials evaluating oral drug use in surgical patients, the long half-life of these drugs make titration in the face of changing clinical parameters difficult. Furthermore, many of the oral drugs, (e.g., metformin and thiazolidinediones) do not decrease serum glucose but rather increase tissue sensitivity to insulin. Further, sulfonylureas use has been associated with prolonged hypoglycemia requiring continuing interventions especially in patients with hepatic, renal, and adrenal insufficiency.
4. *Provide basal insulin in patients who are insulin-deficient.* Insulin-deficient diabetics should always have basal insulin with either continuous IV insulin or long-acting subcutaneous insulin. In these patients, a sliding scale alone is insufficient. Withholding basal insulin in insulin-deficient individuals has reportedly resulted in an increase in serum glucose by 45 mg/dL per hour (7).
5. *Create and implement a hypoglycemia prevention and management protocol.* Though patients may benefit from tight glucose control, the use of insulin poses the risk for hypoglycemia perioperatively. The Joint Commission on Accreditation of Healthcare Organizations (www.jcaho.org) considers insulin to be one of the five high alert medications, since medication errors involving insulin can have catastrophic consequences. Caregivers using tight glucose control protocols must educate caregivers to recognize signs of hypoglycemia, understand the potential accuracy of finger-stick measurements of glucose, and know appropriate interventions.

Given our increasing knowledge of the science of patient safety, it is unlikely that health care organizations will achieve these perioperative glucose management goals without creating standardized policies and

procedures, educating providers about these policies, and providing clinicians with feedback regarding their performance. Thus, in light of these guidelines, how should the article by Duncan et al. be interpreted? First, we believe this article highlights the likelihood that it is not necessary to cancel cases where patients take metformin up to the morning of surgery, while acknowledging that our estimates of safety allow for the possibility of rare events. Second, when we develop and evaluate interventions to reduce the percent of patients with poor glucose control, oral drugs play a limited role. Rather, clinicians need to start to "think like a pancreas," and seek to improve perioperative glycemic control.

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