Journal of Diabetes Science and Technology
Volume 3, Issue 6, November 2009

SYMPOSIUM

Perioperative Blood Glucose Monitoring in the General Surgical Population

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Abstract

Several studies have shown a relationship between poor outcome and uncontrolled blood glucose (BG) in cardiac, neurosurgical, critical care, and general surgical patients. A major study showed that *tight* glycemic control (80–110mg/dl) was related to increased mortality. Based on evidence from controlled studies, the American Diabetes Association, and the Society of Thoracic Surgeons, maintaining intraoperative BG levels in the 140–180 mg/dl range seems appropriate. Optimization of the patient's preoperative medications and the use of insulin infusions, as well as surgical and anesthetic technique, are important factors for achieving desirable perioperative BG control. Minimizing BG variability during surgery should be part of the glycemic control strategy. Advances in real-time glucose monitoring may soon benefit hospitalized diabetes and nondiabetes patients.

J Diabetes Sci Technol 2009;3(6):1282-1287

Introduction

Inadequate glycemic control in the surgical patient has been shown to increase morbidity and mortality.[1–3] Reports have mainly focused on the cardiac, neurosurgical, and critical care patient. Some of the key findings related to outcome may, however, be applied to the general surgical patient.[4,5] Furthermore, hyperglycemia has been associated with poor clinical outcomes in both diabetes and nondiabetes patients. Diabetes patients are more likely to present as surgical patients with glycemic control challenges.[6] In a retrospective analysis of 179 diabetes patients who had noncardiac surgery, mortality at 1 year was 24%. Predictors of death were ischemic heart disease, urgent surgery, American Society of Anesthesiologists physical status score, and hyperglycemia.[7,8] A high blood glucose (BG) level is one component of anesthetic care that may need more stringent control, as evidenced by many studies, but tight control may also have negative outcomes as shown in the data from the Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study.[9]

NICE-SUGAR is a large multicenter study published in April 2009, which included 6104 intensive care unit (ICU) patients in three different countries.[9] Ninety-day mortality was a main outcome measure in which significantly

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Abbreviations: (BG) blood glucose, (GIK) glucose–insulin–potassium, (GLUT) glucose transporter, (ICU) intensive care unit, (IIT) intensive insulin therapy, (NICE-SUGAR) Normoglycemia in Intensive Care Evalution-Survival Using Glucose Algorithm Regulation, (NPO) *nil per os,*

Keywords: diabetes surgical patient, glucose monitoring, glycemic control, hyperglycemia, hypoglycemia, insulin infusion, perioperative

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more patients in the intensive insulin therapy (IIT) group died than in the conventional control group (27.5% versus 24.9%). The IIT group had tight glycemic control, with BG maintained between 80 and 110 mg/dl, compared to 140 and 180 mg/dl in the conventional group. The causes of death were similar between the two groups, but cardiovascular cause was more common in the IIT group. Also, severe hypoglycemia occurred in 6.8% of the IIT group compared to 0.5% of the conventional control group ($p < 0.001$). A meta-analysis that included the NICE-SUGAR study concluded that IIT did not confer an overall mortality benefit among critically ill patients and that it significantly increased the risk of hypoglycemia.[10] Interestingly, the study also reported that patients in the surgical ICU had a better outcome with IIT. Patients from a surgical ICU treated with IIT had a relative risk of death of 0.63 compared with 0.91 in patients from medical ICUs.

Although clinical guidelines have been published for specific in-hospital patient populations, perioperative guidelines from the American Society of Anesthesiologists are still pending. The 2009 American Association of Clinical Endocrinologists/American Diabetes Association consensus statement states that a critically ill patient should be maintained within a BG range of 140–180 mg/dl once insulin therapy has been started, and in a noncritically ill patient, the premeal BG should be less than 140 mg/dl, with random blood sugars of less than 180 mg/dl.[11] Intraoperative glycemic control recommendations from the Society of Thoracic Surgeons indicate that BG of greater than 180 mg/dl should be treated with single or intermittent intravenous insulin and maintained at less than 180 mg/dl.[12]

An optimum target for perioperative BG has not been determined, but a BG of <150 mg/dl is generally considered clinically acceptable, although not always easily achieved.[13] This is explained by the many factors that can lead to hyperglycemia or hypoglycemia. In diabetes and nondiabetes patients, the stress of surgery causes a hyperglycemic response characterized by increased catecholamines, growth hormones, glucagon, and cortisol levels, with a concomitant depression in insulin levels. Hepatic glycogenolysis and gluconeogenesis, along with reduced insulin secretion and tissue insulin resistance, further contribute to the hyperglycemia.[13–15] Hypoglycemia can occur when patients are *nil per os* (NPO) for prolonged periods or are given large doses of insulin. This is particularly detrimental when the symptoms of hypoglycemia are masked by anesthesia during the perioperative period.

The benefits of insulin treatment may stem from its anabolic, anti-inflammatory, and anti-apoptotic effects. In addition, insulin may improve dyslipidemias and prevent endothelial dysfunction and hypercoagualibity in critically ill patients.[1] Stringent glycemic control protocols have been shown to improve infections and other outcome measures for trauma, cardiac, and critically ill nondiabetes surgical patients. On the other hand, some believe that the initial hyperglycemic response in critical illness is a protective and adaptive response, which serves to deliver glucose to poorly perfused hypermetabolic tissues.[7,16–18] Cardiac function is highly dependent on glucose and lipids for myocardial energy, and with high concentrations of insulin, the hyperglycemic and hyperlipidemic responses to stress are prevented. These energy sources are especially needed during reperfusion of the myocardium.[19]

Preoperative Blood Glucose Effects on Intraoperative Care

Hemoglobin A1c, oral hypoglycemics, and insulin regimen all play a major factor in intraoperative glycemic control. Although there are no set guidelines for preoperative glucose levels, some important conclusions can be drawn from current research. All diabetes patients, even if diet-controlled, should have a preoperative fasting glucose, and when glucose concentration exceeds 180 mg/dl, clinicians should initiate insulin therapy.[6,8,11]

A hemoglobin A1c that is <7% is often associated with evidence of good long-term glucose control and has also been demonstrated to decrease the rate of infectious complications across a variety of surgical procedures.[20] Hemoglobin A1c levels ≥7% may indicate poor control, and elevated BG levels in those patients may require slower reduction in BG with more vigilant monitoring. Biguanides, sulfonylureas, and thiazolidinediones have not been studied in the perioperative period, mainly because of the risks of hypoglycemia. Diabetes patients are asked to discontinue these medications at least 24 h prior to surgery, knowing that anesthesia and surgical stress may present an added risk.[13] It should be noted that, when patients present for emergency surgery, without discontinuation of oral medications, they are at greater risk for complications. For example, biguanide therapy should be stopped 48 h before surgery, as it may lead to lactic acidosis, renal failure, and hepatic failure in the hypoperfused state.[13,21,22] Sulfonylureas have a potassium-channel-blocking effect that may interfere with myocardial ischemia preconditioning.[23,24] It has been shown that patients who are undergoing coronary

angioplasty and are receiving sulfonylureas have greater mortality than those receiving insulin.[13] Furthermore, mortality was significantly higher among diabetes patients treated with sulfonylurea drugs at the time of myocardial infarction (24% versus 11%).[25]

With the introduction of different types of insulin and improved glucose monitoring, preoperative insulin regimens have changed. The traditional administration of one half of the insulin dose on the morning of surgery may not be appropriate. While patients are NPO, preoperative BG should be checked and controlled with short-acting insulin. Surgical patients on a basal insulin (e.g., glargine) should be maintained on their dose, even on the day of surgery. While NPO, it may become necessary to infuse dextrose 5% and follow BG at least hourly.[26]

It is not clear what level of glycemic control is associated with the best risk–benefit ratio for diabetes patients or what protocol for BG measurements should be followed, but we do know that intraoperative insulin infusions can reverse some of the undesirable metabolic effects of hyperglycemia.[13,27] Long-term intensive BG control has also been shown to decrease the risk of microvascular[28–29] and macrovascular complications.[30] Dietary carbohydrate restriction may be the best recommended method of BG control in diabetes patients since it is generally not associated with hypoglycemic episodes. It is also a more efficient way of controlling hyperglycemia since insulin activity involves the glucose transporter (GLUT)4, but not GLUT1 transporters.[31,32] The total BG concentration can be lowered by insulin, but there can be hyperglycemic tissues that remain a source of toxicity.

Intravenous infusions are the preferred method of perioperative insulin administration. Lazar and colleagues[12] allocated patients to tight glycemic control using a glucose–insulin–potassium (GIK) infusion or standard therapy using intermittent subcutaneous insulin. Both regimens were initiated before anesthesia and continued for 12 h after surgery. Diabetes patients who received a short course of GIK had a lower incidence of atrial fibrillation, shorter postoperative stay, fewer recurrent wound infections, and fewer episodes of recurrent ischemia, with better survival rates for 2 years after surgery.[12] Studies have shown that continuous insulin infusions provide better glucose control, whether using GIK or continuous insulin infusions. The latter may be a more attractive method, as adjustments to insulin can be made without replacing the bag. Combined glucose, insulin, and potassium solutions have been advocated for many years and have the advantage of inherent safety; however, separate infusions may provide better control and are likely to be more accepted by nursing staff.[6,13,33,34]

Not only have studies shown that hypoglycemia or hyperglycemia may be detrimental, but increased BG variability may also play an important role with respect to complications and outcome. A large retrospective observational study by Egi and associates showed that decreased BG variability in the critical care setting was an independent predictor of lower ICU and hospital mortality.[35]

There are surgical and anesthetic techniques that can minimize the stress of surgery and therefore minimize the hyperglycemic response. These include minimally invasive surgeries and neuraxial anesthesia.[7,36,37] Surgery itself causes a reduction in insulin sensitivity, which is proportional to the length and technique of the procedure. Thorell and coworkers[37] demonstrated that cholecystectomy preformed as a laparoscopy caused significantly less reduction in insulin sensitivity compared to that of a conventional open surgical technique. General anesthesia resulted in release of a greater concentration of stress hormones compared to local and epidural anesthesia. Also, volatile anesthetics used for induction and maintenance of general anesthesia inhibit insulin secretion and increase hepatic glucose production, therefore elevating BG levels.[6] Glucose control prior to surgery should facilitate better intraoperative management. Achieving normoglycemia during surgery is difficult in diabetes patients when initial BG values are in the 300 mg/dl and above range.[7]

Outcomes Studies on Perioperative Glucose Management

Although there are no studies examining the effect of intraoperative BG on outcome in the general surgical population, it is evident that the attention given to perioperative BG control arose from the growing number of outcome studies in critically ill patients.[1,35,38,39] Tighter glycemic control in cardiothoracic surgical patients with diabetes has been associated with improved morbidity and mortality.[40–42] The risk of postoperative infection was found to be directly related to the perioperative BG values rather than hemoglobin A1c.[13,43] Postoperative BG values in cardiac surgical patients have now become a core measure set by The Joint Commission.[4] Interestingly, other studies[44,45] have shown no benefit from tight glycemic control in critically ill patients, but it is difficult to assess their significance on perioperative BG control at this time.

Postoperative hyperglycemia in diabetes or nondiabetes patients has been associated with an increased risk of 30-day postoperative infectious complications and a longer hospital stay. Every 40 mg/dl increase in postoperative glucose led to a 30% increased risk of postoperative infection.[5] Randomized controlled trials in medical, cardiac, and neurosurgical populations have found reduced rates of bacteremia, duration of antibiotic usage, infections rates, and incidence of recurrent infections in patients having strict glycemic control (<150 mg/dl). The Portland glucose control protocol targets a BG < 150 mg/dl in diabetes patients undergoing cardiac surgery. Studies have shown reduced rates of infection in the acute postoperative period with this BG target.[5,40,41] Although multiple BG protocols have been developed,[5,46–49] there is a paucity of clinical evidence on the effect of BG control in stress-induced hyperglycemia on diabetes and nondiabetes patients. Defined parameters for intraoperative BG management are still lacking,[5,50,51] while there is also controversy over the safety and efficacy of IIT in acute care settings. Studies have been stopped prematurely due to a high incidence of severe hypoglycemia and other serious adverse events. Some studies have shown that intraoperative IIT in cardiac surgery may increase the incidence of death and stroke.[4,52–54]

Monitoring Devices

Most studies on BG management in acute care settings support the use of continuous insulin infusion as a means to achieving glucose control; however, current glucose monitoring technology still has limitations. It has been suggested that, with increased availability of continuous glucose monitoring devices, safer glycemic control may be achieved with decreased risk of hypoglycemia.[55]

A study conducted in critically ill patients using three glucometers, including the Accu-Chek, reported an ~14% rate of inaccurate readings compared to a validated glucose oxidase reference method.[56] The inaccuracy occurred overthe entire range of BG values. The patients who demonstrated the greater incidence of inaccurate measurements were the elderly and those with a higher disease severity score. Interestingly, those patients had a higher ICU mortality compared to patients with accurate glucose values. Glucometers may have up to a 20% error and were not intended for intensive care use and administration of IIT. In anemic patients, the measurement error may be up to 30% compared to laboratory values.[57] Although the technology has improved, there are differences in performance between those meters.

Subcutaneous glucose sensors for continuous glucose monitoring have become available, such as the CGMS Gold (Medtronic MiniMed, Sylmar CA), the Navigator (Abbott Laboratories, Abbott Park, IL), and the Dexcom Seven (Dexcom Inc., San Diego, CA). A study showed the CGMS Gold to have strong correlations to actual BG and found it to be an important tool in adjusting insulin therapy in ICU patients.[58,59] Although encouraging, those glucose sensors generally have not demonstrated the needed accuracy in the acute care setting, which partly explains why they are not widely used in hospitalized surgical and ICU patients. Those sensors have been approved for 3–7 days of use but still require frequent calibrations from the patient's blood. On the other hand, valuable information has been gathered from these sensors on BG patterns, hypoglycemia, and BG variability. More studies are being conducted on these devices, and more accurate versions may be more readily available in the near future.

Conclusion

Postoperative hyperglycemia is associated with an increased risk of 30-day postoperative infectious complications and a longer hospital stay, independent of diabetes.[5] Current evidence and recommendations support increased vigilance with glycemic control, which should reduce or prevent morbidity in the general surgical patient. Diabetes surgical patients will need more stringent control, starting with preoperative glucose measurements, as well as strict intraoperative BG monitoring. If glucose is elevated more than 180 mg/dl, then insulin therapy should be started preoperatively. During surgery, diabetes patients' BG should be maintained in the 140–180 mg/dl range, preferably using a protocol to ensure safe insulin titration, especially with respect to hypoglycemia and large BG fluctuations (variability). For nondiabetes patients undergoing high-risk surgical procedures, a significant stress response can be mounted with elevations in BG. In those patients, we support the practice of targeting BG levels to less than 150 mg/dl, with frequent BG measurements. Tight glucose control in the perioperative period awaits further advances in real-time monitoring technology and treatment protocols but promises to benefit hospitalized diabetes and nondiabetes patients.

Disclosure:

Dr. Torjman serves as a consultant on IntelliDx, Inc.'s Scientific Advisory Board.

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