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SYMPOSIUM

Perioperative and Critical Illness Dysglycemia—Controlling the Iceberg

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Abstract

Patients with dysglycemia related to known or unrecognized diabetes, stress hyperglycemia, or hypoglycemia in the presence or absence of exogenous insulin routinely require care during the perioperative period or critical illness. Recent single and multicenter studies, a large multinational study, and three meta-analyses evaluated the safety of routine tight glycemic control (80–110 mg/dl) in critically ill adults. Results led to a call for more modest treatment goals (initiation of insulin at a blood glucose >180 mg/dl with a goal of ~150 mg/dl). In this symposium, an international group of multidisciplinary experts discusses the role of tight glycemic control, glucose measurement technique and its accuracy, glucose variability, hypoglycemia, and innovative methods to facilitate glucose homeostasis in this heterogeneous patient population.

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The epidemic of type 2 diabetes mellitus (T2DM) continues to grow despite enhanced awareness and efforts to control its progression. Current estimates place the prevalence at 12.9% of those over 20 years of age in the United States.[1] Projections for the lifetime risk of development of T2DM are as high as 32 to 52% for children born after 2000 depending on gender, ethnicity, and environmental factors.[2] The staggering implications for quality of life and health care costs drive efforts across all fields of medicine to identify, stratify, optimally manage, and monitor the dysglycemic patient.

Recognized T2DM is only the tip of the perioperative dysglycemic iceberg given that an estimated 40% of those with T2DM are unaware of their diabetes and remain undiagnosed.[1] Furthermore, a large number of adult perioperative patients have impaired fasting glucose (25.7%) or impaired glucose tolerance (13.8%).[1] A significant, but currently not quantified, number of perioperative patients develop stress-induced hyperglycemia intraoperatively, postoperatively, or during their intensive care unit (ICU) course.[3] The natural history of stress-induced hyperglycemia also remains unclear, and it is uncertain as to whether it increases the risk for later development of T2DM. Finally, tighter glucose control regimens in critically ill patients have been associated with a significant incidence of hypoglycemia (defined as moderate at 40–60 mg/dl and severe at <40 mg/dl). Hypoglycemia has a deleterious impact on ICU patient survival, even if insulin is not infused. This has led to a

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Abbreviations: (ICU) intensive care unit, (NICE-SUGAR) Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation, (T2DM) type 2 diabetes mellitus

Keywords: critically ill, dysglycemia, glucose measurement, guidelines, hospitalized patients, hypoglycemia, stress-induced hyperglycemia, type 2 diabetes mellitus

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revision of hospital-based glucose control guidelines by the American Association of Clinical Endocrinologists and the American Diabetes Association.[4]

The ageing of the U.S. population has been associated with the need for frequent procedural interventions and the requirement for critical care for a host of acute pathologies. Physicians involved in perioperative and critical care medicine are certain to encounter patients with known or unrecognized acute or chronic dysglycemia defined as hyperglycemia (be it related to known or previously undiagnosed diabetes or stress) or hypoglycemia in the presence or absence of insulin. Clinicians require more reliable methods to identify those with, or at risk for, perioperative dysglycemia. Screening for T2DM is increasingly called for, but the best method to identify its presence remains controversial.[5–9] Also, more information is needed regarding the impact of chronic glucose control during the perioperative period and on those who are critically ill. The potential risk/benefit of improving chronic glucose control prior to elective surgical or procedural interventions needs further investigation.[10–15]

Since Van den Berghe and colleagues in a single center study reported the benefits of normalization of glucose levels in extended stay ICU patients who were actively nourished and predominantly admitted after cardiac surgery, a large body of oft-conflicting literature has been produced evaluating glycemic control in perioperative and critically ill patients.[16–23] Attempts to address optimal glucose goals in perioperative or critically ill patients, timing of initiation of glucose control, risk factors for and the dangers of hypoglycemia, effect of glucose variability, impact of premorbid diabetes, presence of undiagnosed diabetes, and role of stress-induced hyperglycemia upon outcome remain under investigation.[16–18,20–31] Despite the absence of clear answers to these issues, various regulatory bodies and learned medical organizations and societies increasingly called for normalization of glucose levels in critically ill patients and often include intraoperative and postoperative patients in their recommendations. Proposals for the basing of reimbursement on the level of glucose control have also been considered.[32–36] With the publication of the Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial in March 2009 and a subsequent meta-analysis of glucose control in the ICU, we have more cautionary data that call for less aggressive normalization of glucose in the acutely stressed perioperative or critically ill patient.[30,37] With an enrollment of 6104 patients between December 2004 and November 2008, NICE-SUGAR was the second largest trial ever performed in adult ICU patients. Interestingly, tight glucose control (goal of 80–110 mg/dl) using a standardized protocol across academic and community centers in Australia, New Zealand, Canada, and America resulted in increased mortality when compared to the "conventional group" whose goal was 144–180 mg/dl.[37,38] The incidence of hypoglycemia was significantly higher in the tightly controlled group (6.8%) versus the conventional group (0.5%), but in keeping with or lower than the incidence found in other major glucose control trials. NICE-SUGAR provided tremendous information, but raised more questions about glucose monitoring and stimulated further discussion as to whether tight control might improve outcomes if hypoglycemia could be avoided.[38–45] A revised recommendation was recently issued by the Surviving Sepsis Campaign Guidelines Committee Subgroup for Glucose Control not to initiate insulin therapy when glucose levels are <180 mg/dl in patients with severe sepsis. In those patients, glucose levels should now be maintained at about 150 mg/dl.[46]

The challenging topic of glucose control in the perioperative and critically ill patient reminds us of the need for caution in interpreting single center studies, particularly if they present findings that may be center specific or if the findings are especially strong and call for patience while awaiting additional corroboration. Further, an interdisciplinary approach to management of the complex perioperative patient is needed. The reports and reviews included in this symposium draw from a collection of expert international investigators with specific interest in preoperative assessment and preparation, intraoperative management, and critical care of medical, surgical, cardiothoracic, coronary, burn, transplant, trauma, and neurologically compromised patients. The authors of the articles include endocrinologists, hospitalists, surgeons, internists, anesthesiologists, critical care physicians, and other researchers involved in best practices for glucose measurement and management.

This symposium calls to our attention the fact that a "one-size fits all" approach to dysglycemia in the heterogenous perioperative and ICU populations may not be warranted and should be undertaken with care. The authors provide current recommendations to identify patients at risk for perioperative and ICU-associated dysglycemia, focus on specialized patient populations, highlight the dangers of even brief and single episodes of hypoglycemia, and discuss evolving techniques to measure glucose and maintain reasonable glucose control. The routine normalization of glucose levels during the brief—usually 4–8 hours maximum—but dynamic

intraoperative period may be ill- advised.[47] A host of factors, including temperature, anemia, perfusion, and the presence of interfering substances, may affect the accuracy of intraoperative or ICU glucose measurements and mislead the clinician in adjusting insulin infusions. Further, end-organ dysfunction may impact insulin dynamics or glucose regulatory responses during anesthesia and surgery.

Discussion of the differences in benefits of glucose control across specific populations, including those with diabetes, those with unrecognized diabetes, or those with stress-induced hyperglycemia, reminds us that dysglycemia is a heterogenous iceberg with some common features, but also elements unique to the causative process. The fascinating topic of glucose variability in the critically ill further calls into question the role of the absolute goal for control in various populations versus the role of variability even within groups considered to be within the "normal" range of laboratory values. To that end, two leading groups of glucose control investigators share their perspective on glucose variability. They highlight potential mechanisms of how variability may influence outcome and how more information is needed about the impact of variability on outcome if there continues to be wide swings after glucose has normalized or if marked variability develops during the course of critical illness after initial stabilization.

Ultimately, the goal is the development of standards that will facilitate identification and stratification of perioperative dysglycemia across various hospital populations possibly corroborated by individual genomic assessment of markers of abnormal glucose metabolism, inflammation, and stress. Clinicians should be able to apply safe and reliable glucose measurement techniques utilizing optimal modes/protocols for the maintenance or favorable modulation of glucose homeostasis to individualize care of the dysglycemic patient. Finally, appropriate follow-up of patients with dysglycemia in the perioperative period or in the critically ill provides a means to initiate therapies that will hopefully favorably impact long-term quality of life and survival.

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