

Invited Commentary

Glucose Control and Its Implications for the General Surgeon

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THERE HAS BEEN AN INCREASING amount of literature over the last few years describing the importance of glucose control in hospitalized patients. Normalization of blood glucose levels in both diabetic and nondiabetic patients has been proposed to improve outcome and reduce the short term and long term adverse consequences of hyperglycemia. Several regulatory or advisory groups have even promoted tight glucose control as a process that should be monitored in critically ill patients to assess the quality of care.¹ The American Diabetes Association has published guidelines on standards for blood glucose control in diabetic and critically ill patients that have been incorporated into benchmarks used by the Joint Commission's certification program for Disease Specific Care regarding the inpatient management of diabetes.^{2, 3} Many surgeons may therefore have experienced the adoption of glucose control protocols in their hospitals and Intensive Care Units (ICUs) as the wave of enthusiasm for normalization of glucose levels has gained momentum. When the practice of normalization or near-normalization of blood glucose levels is applied to nondiabetic patients in the critical care environment, this phenomenon is referred to as either Intensive Insulin Therapy or Tight Glycemic Control. These terms are used interchangeably in the literature. It is important to keep in mind, however, that few of the seminal findings in the field of tight glucose control in critically ill adults have been directly tested in the patient populations served by most general surgeons. The evaluation of Tight Glycemic Control is ongoing and new studies are being published on a regular basis. This review is designed to inform and update the practicing general surgeon on this important topic and summarize the current status in this rapidly changing field.

Adverse Effects of Hyperglycemia

Tightly controlling glucose levels in patients with diabetes mellitus is thought to reduce the risk of

cardiovascular disease and death.⁴ It therefore makes intuitive sense that tightly controlling glucose levels may prevent other types of complications of hyperglycemia in different groups of patients. Hyperglycemia has a number of physiologic and cellular effects that can potentially interfere with the short- and long-term function of cells and tissues. Hyperglycemia can inhibit smooth muscle function and decrease vascular reactivity.⁵ Hyperglycemia can also interfere with polymorphonuclear cell phagocytosis and chemotaxis, increase cellular oxidative stress, decrease collagen synthesis, and interfere with peripheral nerve function.^{5, 6} These cellular effects of hyperglycemia have been postulated to alter host immune defense, wound healing, and vital organ function. Hyperglycemia has also been linked to adverse clinical outcomes. Hyperglycemia has been associated with increased mortality in patients with myocardial infarction, worse outcome after stroke, and increased mortality in hospitalized adults.⁷⁻¹¹ Admission hyperglycemia has also been associated with increased morbidity and mortality after injury.¹²⁻¹⁶ It is a plausible hypothesis, therefore, that better control of glucose might reverse some of the deleterious consequences of hyperglycemia. The studies discussed above, however, demonstrate associations between hyperglycemia and outcome but do not establish a cause/effect relationship. Glucose mobilization, increased gluconeogenesis, and hyperglycemia are normal components of the host stress response.¹⁷ None of these studies can define whether hyperglycemia is the cause of poor outcome or simply a reflection of the magnitude of the counter-regulatory response of the body to severe illness, injury, or infection.¹⁷⁻²⁰

Intensive Insulin Therapy-Pro

The Van den Berghe et al.²¹ study on tight glucose control in critically ill adults ignited the controversy in this area and has been the most widely cited study on intensive insulin therapy. This study was a randomized, prospective single institution investigation in which the authors found a significant reduction in mortality with tight glucose control (4.6% mortality with blood glucose levels of 80-110 mg/dL) compared

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with conventionally treated patients (8.0% mortality with glucose levels of 180–200 mg/dL).²¹ Decreased renal dysfunction, decreased blood transfusions, decreased rate of sepsis, and decreased percentage of patients requiring > 14 days of ICU care were also findings present in the tightly controlled group.²¹ This study was widely cited as proof that a simple, readily available intervention could dramatically improve outcome for critically ill patients. Several large retrospective or prospective observational studies were subsequently published and supported the benefits of intensive insulin therapy to tightly control glucose levels in critically ill patients.^{22–24} A second prospective, randomized trial was performed by Van den Berghe et al.²⁵ in medical ICU patients. The authors found decreased renal dysfunction, earlier weaning from mechanical ventilation, earlier ICU discharge, and earlier hospital discharge in the tightly controlled patients although the overall mortality rate was unchanged.²⁵ In a subgroup analysis, the authors found a mortality benefit associated with normalization of glucose levels for patients who required greater than 3 days of ICU care.²⁵ For patients who stayed less than 3 days in the ICU, though, tight glucose control was associated with increased mortality.²⁵ A number of biologic mechanisms for the apparent improvement in outcome associated with tight glucose control have been proposed including a reduction in the polyneuropathy of critical illness that could interfere with weaning from mechanical ventilation, improved cellular energy utilization, and improved overall metabolic control.^{26–29} Intensive insulin therapy has been proposed to also reduce overall health care expenditures, presumably through its effects on ICU length of stay and duration of mechanical ventilation.^{30, 31}

Intensive Insulin Therapy-Con

The ability of intensive insulin therapy to improve outcome in other critically ill patient populations has been met with mixed results. In critically ill general surgery, trauma, and burn patients, tight glycemic control has been associated with decreased infectious morbidity and decreased mortality,^{32–34} decreased infectious morbidity with no effect on mortality,^{35, 36} and no effect on either infectious morbidity or mortality.^{37, 38} Unfortunately, none of the above studies were prospective randomized trials and the reasons for such disparate results are not clear. Variability in glucose management protocols, glucose target ranges, and the effectiveness (or lack thereof) of reaching target goals may all play a role. Technical factors such as the time of glucose sampling or the method used to measure glucose can also affect the glucose values and the accuracy of reaching the target range.^{39–42} In

addition, factors such as the baseline intensive care unit mortality, baseline patient glucose values, and patient mix can all contribute to a variable effect of implementing a tight glucose control policy on mortality in any particular ICU.⁴³

The importance of patient characteristics and local ICU practice patterns have raised questions about the applicability of the findings of the single institution randomized trials of tight glucose control to different ICU environments.^{1, 43–46} Krinsley²⁴ studied predominantly medical patients, whereas the majority of surgical patients in the prospective studies by Finney et al.²³ and Van den Berghe et al.²¹ were cardiac surgery patients. Whether the findings of these studies can be replicated in general surgery, trauma, and burn patients has not been thoroughly tested. In addition, several factors regarding the patients and practice patterns in the Van den Berghe studies suggest that the results of their investigations may not be relevant to ICU patients in different critical care environments. Factors present in the Van den Berghe studies that may be unique to their ICU include the routine early administration of total parenteral nutrition, the high mortality of conventionally treated cardiac surgery patients despite relatively low APACHE scores, and the relatively high mortality benefit attributed to glucose control compared with other factors that influence mortality after cardiac surgery.^{1, 43–46} It is also difficult to explain why the beneficial effects of tight glucose control on ICU survival, ICU discharge, and weaning from mechanical ventilation in the Van den Berghe studies do not begin to appear until approximately 20 to 25 days after admission in a group of patients where few had ICU stays exceeding 14 days.^{21, 25} Furthermore, the increase in mortality in the tightly controlled medical ICU patients that stayed less than 3 days in the ICU²⁵ represents an important concern because at the time of ICU admission, the ability to predict which patient will require a brief ICU stay is limited.

Recently, several randomized controlled trials have been unable to confirm the findings of the Van den Berghe studies. Intensive insulin therapy had no effect on mortality or organ failure in patients with sepsis in a multicenter trial enrolling patients admitted to European ICUs but was associated with a higher incidence of hypoglycemia.⁴⁷ This trial was stopped before completing the planned patient accrual due to lack of benefit for tight glucose control which was similar to another European trial on intensive insulin therapy called GLUCONTROL.^{44, 47} A lack of efficacy with respect to mortality was seen in a recent randomized controlled trial of mixed medical/surgical ICU patients⁴⁸ and in a pre/post intervention observational study.⁴⁹ A meta-analysis of all randomized controlled trials on intensive insulin therapy likewise failed to

identify a mortality benefit for tight glycemic control in critically ill patients.⁵⁰ Although hyperglycemia is postulated to induce secondary brain injury and has been associated with worse neurologic outcome,^{9, 51} tight glucose control is associated with decreased cerebral glucose availability and cellular injury.⁵² Interestingly, the studies questioning the value of tight glucose control in critically ill patients are emerging as the benefit of tight control in diabetes is also being reexamined.^{53, 54}

Although the benefit on mortality, if any, seems to be less than originally thought, varies depending on the ICU environment, and potentially is nonexistent, a common finding in all tight glucose control trials is that intensive insulin therapy is associated with an increased frequency of hypoglycemia.^{21, 22, 25, 43, 47-50} Although the adverse clinical consequences of hypoglycemia in these trials have been difficult to define and may vary depending on the target range of glucose selected as a goal, hypoglycemia independently increases the risk of mortality in critically ill patients.⁵⁵ Adverse metabolic effects of normoglycemia in susceptible critically ill patients who may depend on higher glucose levels to support a higher cellular metabolic rate^{51, 52} suggests that caution needs to be applied, particularly in populations of critically ill patients that have not been represented in the randomized controlled trials published to date.

Recently, the concept of glucose variability has been promoted as an important clinical factor. Glucose variability attempts to define the fluctuations in glucose values that can occur in an individual patient over time as an index of deviation from normal homeostasis. Although "variability" can be defined in different ways, and some degree of variability may be normal,³⁹ studies have suggested that fluctuations in glucose homeostasis, as opposed to absolute glucose levels, may be important determinants of mortality in critically ill patients.⁵⁶⁻⁵⁹ These studies emphasize that the magnitude of the disturbance in normal homeostasis may be an important determinant of outcome in critically ill patients. Unfortunately, these provocative studies do not answer the important biologic question of whether the abnormalities in glucose homeostasis cause the complications associated with critical illness or whether the abnormalities of glucose homeostasis are simply a reflection of the altered host response to critical illness that also determines complications, length of stay, and mortality.

Summary

In the face of these conflicting data, how should the practicing surgeon approach the issue of tight glucose control in their critically ill surgical patients? The

answer to that question may well change over time as new data emerge. For now, however, it seems reasonable to conclude that tight glucose control to the normal range (80–110 mg/dL) in critically ill general surgery patients (i.e., the Van den Berghe model) is an intriguing but unproven hypothesis that needs to be confirmed by prospective randomized trials in different ICUs and in a relevant patient population. It is quite possible, and probably likely, that levels of hyperglycemia that were previously thought to be inconsequential (180–200 mg/dL) may be harmful when sustained over prolonged periods of time and that better glucose control in the ICU than previously practiced is merited. However, given the detrimental effects of hypoglycemia,^{50, 55} great care must be exercised in trying to achieve better glucose control so as not to induce harm. Technical considerations such as differences in glucose measuring systems, use of morning *versus* all glucose values, and nutritional regimens all need to be considered. The ICU is by definition a complex environment involving multiple teams of consulting specialists whose orders for medications, dialysis treatments, radiographic studies, and interruptions of enteral nutrition may all disrupt the ability to establish stable blood glucose levels. These factors need to be accounted for in daily clinical practice and their roles need to be better understood in future clinical trials. At present, it seems reasonable to attempt to control blood glucose levels in critically ill general surgery patients to moderate levels that avoid deleterious hypoglycemia but have been associated with encouraging clinical results until better data emerge. Until that time, the clinician will need to attempt to balance the potentially detrimental effects of hyperglycemia with the risk of hypoglycemia carefully until future trials involving general surgery patients are completed to clarify this issue.

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