

## **Critical Care Review: the High Price of Sugar**

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### ***Abstract***

The intensive control of blood glucose had been proposed to be important in increasing survival in the intensive care unit (ICU) despite only one positive randomized trial. The concept was supported by guidelines released by several regulatory organizations including the Joint Commission of Healthcare Organizations and the Institute of Healthcare Improvement. However, the large, randomized, multi-center NICE-SUGAR trial published in 2009 showed tight control of glucose in the ICU is actually hazardous with a 14% increase in mortality. The historical basis and data used to support intense control of glucose in the ICU are reviewed and illustrate the harm that can result when guidelines are based on weak evidence.

### ***Intensive Control of Glucose in Diabetes***

Diabetes has long been associated with vascular complications. These are divided into microvascular complications (retinopathy, nephropathy, and neuropathy) and macrovascular complications (coronary artery disease, stroke, and peripheral vascular disease). The concept that intense control of glucose results in improved vascular outcomes in diabetes dates back decades but has been plagued with controversy. The University Group Diabetes Program Study (UGDPS), which began in 1959, was designed to evaluate the relationship between blood sugar control and vascular complications in patients with newly diagnosed type II diabetes. The investigators found that control of blood sugar levels was ineffective in preventing the micro- and macrovascular complications associated with diabetes, regardless of the type of therapy (1). This prompted the American Diabetes Association (ADA) and the American Medical Association to withdraw their support of UDGPS (2). In 1978, at a meeting of diabetes researchers, clinicians, and epidemiologists from the ADA, the National Institutes of Health (NIH), the Centers for Disease Control, and various university centers, it was concluded that there was “no definite evidence that treatment to regulate blood sugar levels is effective beyond relieving symptoms and controlling acute metabolic disturbances” (2).

This controversy prompted the NIH to organize the Diabetes Control and Complications Trial. This was a large, multi-center, randomized study which compared intensive to conventional treatment in preventing vascular complications in insulin-dependent, type I diabetics. Published in 1993, the results of this trial demonstrated that intensive therapy effectively delayed the

onset and slowed the progression of diabetic retinopathy, nephropathy, and neuropathy in patients with insulin-dependent diabetes (3). However, the mortality rate, incidence of macrovascular complications, and incidence of diabetic ketoacidosis were not significantly reduced. Weight gain and episodes of hypoglycemia were significantly more common in the intensive therapy group.

Published in 1998 but started in 1977, the UK Prospective Diabetes Study (UKPDS) was designed to determine if intensive blood glucose control reduced the risk of micro- or macrovascular complications in type II diabetes (4). This study is important since over 90% of adult diabetics, including the majority of diabetics in an adult ICU, have type II diabetes. This large, multi-center, randomized study compared conventional therapy with diet alone to an intense glucose control with diet and either a sulphonylurea (chlorpropamide, glibenclamide, or glipizide) or insulin. The goals of the study were to maintain fasting blood glucose of less than 270 mg/dL (15 mmol/L) in the conventional group and less than 108 mg/dL (6 mmol/L) in the intensive control group. Consistent with the blood sugar goals of the study, the hemoglobin A1C was reduced in the intensive therapy group compared to the conventional group (7.0% vs. 7.9%,  $p < 0.05$ ). The results in this study of type II diabetics were similar to the Diabetes Control and Complications Trial in type I diabetics. Microvascular complications, particularly retinal complications, were significantly reduced in the intensive therapy group but macrovascular complications were not. Mortality was not reduced and hypoglycemia and weight gain were more common in the intensive therapy group.

### ***Intensive Control of Blood Glucose in the ICU***

Hyperglycemia associated with insulin resistance is common in critically ill patients, even those who have not previously had diabetes (5-7). It had been reported that pronounced hyperglycemia might lead to complications. For example, studies reported that in acute myocardial infarction therapy to maintain blood glucose below 215 mg/dL (11.9 mmol/L) improved long-term outcomes (8-10). Furthermore, high serum levels of insulin-like growth factor-binding protein 1, which reflect insulin resistance, increase the risk of death (11, 12).

Spurred by the above data and the overwhelming opinion of diabetes experts that intensive control of glucose improves outcomes in diabetes and should in the ICU, van den Berge *et al.* (13) compared intensive insulin therapy (maintenance of blood glucose at a level between 80 and 110 mg/dL) to conventional treatment (infusion of insulin only if the blood glucose level exceeded 215 mg/dL and maintenance of glucose at a level between 180 and 200 mg/dL) in ICU patients. The study was large with 1548 subjects but was a single center study from a surgical intensive care unit with 63% of the patients post-cardiac surgery. Reported in 2001, the results showed that intensive insulin therapy reduced mortality during intensive care from 8.0 percent with conventional treatment to 4.6 percent ( $p < 0.04$ ). The benefit of intensive insulin therapy was attributable to

its effect on mortality among patients who remained in the intensive care unit for more than five days (20.2 percent with conventional treatment, as compared with 10.6 percent with intensive insulin therapy;  $p=0.005$ ).

The results of van den Berge's original study were supported by a nonrandomized, single center study reported by Krinsley (14) in 2004. This study from a combined 14 bed medical/surgical ICU consisted of 800 consecutive patients after initiation of an intensive control protocol compared to 800 patients admitted immediately preceding initiation, i.e., a before and after design. The protocol involved intensive monitoring and treatment to maintain plasma glucose values lower than 140 mg/dL. Hospital mortality decreased 29.3% ( $p=0.002$ ), and length of stay in the ICU decreased 10.8% ( $p=0.01$ ) with intensive control of glucose. Despite the before and after comparison, some considered this single center study as confirmatory evidence for the mortality benefit of intensive glucose control.

It has been pointed out that van den Berge's study had multiple limitations (15). Van den Berge's 2001 study was a non-blinded, single center and including predominately patients after cardiac surgery. Other limitations included the unusual practices of most patients receiving intravenous glucose on arrival at the intensive care unit (ICU) at 200 to 300 g/d (the equivalent of 2-3 L of 10% glucose per day) and initiation of total parenteral nutrition, or enteral feeding, or combined feeding for all patients within 24 hours. Also, the mortality of cardiac surgery patients in the control group was 5.1% which is unacceptably high in most centers.

Kringsley's study also had limitations (15). This was a single-center, retrospective, unblinded study and likely reflect a powerful Hawthorne effect (intense glucose control = investigator commitment and bedside presence, more tests, more attention, more patient visits, more interventions, and overall better care). Intensive insulin therapy comes at a substantial price: a greater than 6-fold increase in the risk of hypoglycemia and a marked increase in bedside nurse workload.

When many regulatory guidelines were initiated in the mid 2000's, not all data about glucose control and insulin in acute illness pointed to a benefit. The Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) 2 study with more than 1000 randomized patients with myocardial infarction to intense compared to conventional glucose control failed to show a mortality benefit (16). Similarly, the Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation (CREATE)-Estudios Cardiologicas Latin America Study Group (ECLA) study with over 20,000 randomized patients with myocardial infarction failed to show a benefit of a glucose, insulin and potassium infusion regimen compared to usual care (17).

### ***Regulatory Guidelines***

By 2005 the Joint Commission on Accreditation of Healthcare Organization (Joint Commission) and the Institute for Healthcare Improvement (IHI) recommended tight glucose control for the critically ill as a core quality of care measure for all U.S. hospitals (18). Furthermore, an international initiative by several professional societies, including the American Thoracic Society, promoted a care “bundle” for severe sepsis that also includes intensive glycemic control.

### ***Concerns about Intensive Glucose Control in the ICU***

The medical literature is rife with initially positive trials followed by studies with equivocal or negative trials and occasionally followed by studies with actual harm to patients (19). Intensive control of glucose is a good example of this progression in medical research.

In late 2005, editorials urged waiting on further studies before widespread implement of tight control of glucose as usual care in the ICU. Bellomo and Egi (17) recommended awaiting the results of two large multi-center, randomized trials of tight control of glucose in the ICU, the GluControl study and the NICE SUGAR study. Angus and Abraham (18) echoed the limitations of van den Berge’s study and also advocated caution in the widespread initiation of intensive glucose control in the ICU.

Van den Berge’s group that initially reported the positive results in surgical ICU patients followed their 2001 publication with a report of medical ICU patients in 2006 (20). In this prospective, randomized study of adult patients admitted to the medical ICU, the authors were unable to reproduce the reduction of in-hospital mortality with intensive glucose control seen in their surgical ICU patients (40.0 vs. 37.3% mortality,  $p=0.33$ ). However, the authors reported a significant improvement in morbidity with a reduction in newly acquired kidney injury, accelerated weaning from mechanical ventilation, and accelerated discharge from the ICU and the hospital. However, among the 433 patients who stayed in the medical ICU for less than three days, mortality was greater among those receiving intensive insulin therapy. Since the mean length of stay in our medical intensive care at the Phoenix VA was a little less than 3 days, many of our group became concerned that intensive control of glucose would not improve mortality and might actually prove harmful.

The GluControl study was undertaken in 2004 to test the hypothesis that intensive control of glucose (80-110 mg/dL) improves survival of patients treated in medical/surgical intensive care units (ICU) compared to a control target of 140-180 mg/dL. Planned enrollment was 3500 subjects but the trial was stopped in 2006 after a little over 1000 subjects because interim analysis revealed numerous protocol violations resulting in hypoglycemia. The results were initially reported as an abstract at the 20th Congress of the European Society of Intensive Care in 2008 and a full length manuscript was published in 2009 (21,22). ICU, 28-day and hospital mortality were similar in both groups. ICU and hospital length of stay were identical. Hypoglycemia defined as a blood

glucose below 40 mg/dL was seen in 8.7% of the intensive therapy group vs. 2.7% in the conventional group.

Further concern about the concept of intensive glucose control was raised by Weiner *et al.* (23) in 2008. They searched the medical literature (MEDLINE, the Cochrane Library, clinical trial registries, reference lists, and abstracts from conferences from both the American Thoracic Society and the Society of Critical Care Medicine) and identified 29 randomized controlled trials totaling 8432 patients. A meta-analysis did not reveal a significant difference between intensive glucose control and usual care overall (21.6% vs. 23.3%) but did reveal an increased risk of hypoglycemia (glucose  $\leq$ 40 mg/dL, 13.7% vs. 2.5%). In fact, the only study that showed a mortality advantage was van den Berge's original study in 2001.

### ***The NICE SUGAR Study***

The landmark NICE SUGAR study (24) was published in the spring of 2009. This large study randomized 6104 patients to either intensive glucose control, with a target blood glucose range of 81 to 108 mg/dL, or conventional glucose control, with a target of  $\leq$ 180 mg/dL. The main finding of the study was that intensive glucose control resulted in a 14% increase in mortality. Furthermore, the adverse treatment effect on mortality did not differ significantly between surgical patients and medical patients. As in previous trials, severe hypoglycemia (blood glucose level  $\leq$ 40 mg/dL) was significantly more common in the intensive-control group (6.8%) compared to the conventional-control group (0.5%,  $p < 0.001$ ). There was no significant difference between the two treatment groups in the median number of days in the ICU or hospital, the median number of days of mechanical ventilation or days of renal-replacement therapy ( $p > 0.05$ , all comparisons).

Follow up data was presented by Egi *et al.* (25) in patients admitted to 2 ICUs. The authors analyzed all those who had a blood glucose of  $\leq$ 81 mg/dL to determine if there was an independent association between hypoglycemia and outcome. Of the 4946 patients admitted to the ICUs, 1109 had at least 1 episode of hypoglycemia. Mortality was higher in these patients (36.6%) compared with 19.7% in the nonhypoglycemic control patients ( $p < 0.001$ ). Mortality increased significantly with increasing severity of hypoglycemia ( $p < 0.001$ ). In fact, a minimum glucose of  $< 36$  mg/dL was associated with over a four-fold increase in ICU mortality compared to a minimum blood sugar of 72-81 mg/dL. After adjustment for insulin therapy, hypoglycemia was independently associated with increased risk of death, cardiovascular death, and death due to infectious disease.

### ***Regulatory Agency Guidelines Following the NICE SUGAR Study***

Following publication of the NICE SUGAR study most regulatory agencies dropped their recommendations for intensive glucose control in the ICU. However, remnants of the concept persist. IHI continues to promote "...effective

glucose control in the intensive care unit (ICU) [which] has been shown to decrease morbidity across a large range of conditions and also to decrease mortality” (26). In another posting entitled “Establish a Glycemic Control Policy in Your ICU” (27) IHI states, “Typically, clinicians’ fear of inducing hypoglycemia is the first obstacle to overcome in launching an improvement effort. Doctors remain wary of inducing hypoglycemia and may not have confidence in selecting appropriate doses. Nurses fear hypoglycemia and remain concerned about protocolized adjustments to intravenous insulin rates of administration. The balance of evidence suggests, however, that once these barriers are addressed, ICU patients receive better care with appropriate glycemic control.” Since hypoglycemia is associated with increased mortality in the ICU (22), this doctor and nurse fear of hypoglycemia seems well founded.

### ***Hyperglycemia***

Even though hypoglycemia is associated with excess mortality, hyperglycemia is also undesirable. As Falciglia *et al.* (28) point out, mortality increases with increasing admission glucose in the ICU. Although this is not the same as saying correcting the hyperglycemia improves mortality, it does suggest that hyperglycemia is undesirable. Furthermore, it has long been known that mortality is increased in patients with myocardial infarction and hyperglycemia (29). However, this increase in mortality with hyperglycemia does not apply to all disease states. For example, hyperglycemia in COPD or liver failure is not associated with increased mortality (28). This may have implications if the patients in a particular ICU population have predominately cardiac, respiratory or liver disease. However, even in this study an increase in mortality was noted with an admission blood sugar of <70 mg/dL to the ICU compared to a blood sugar of 70-100 mg/dL and approximates the mortality seen with an admission glucose of >300 mg/dL.

### ***Conclusions and Recommendations***

Based on the available evidence, we would suggest maintaining blood glucose levels of less than 180-200 mg/dL while avoiding blood sugars less than 80 mg/dL in the ICU. Intensive control of glucose is not evidence based, harmful, and should be discouraged. One might be somewhat more aggressive to maintain the blood sugar below 150 mg/dL in patients who are post-operative cardiac patients or receiving large infusions of glucose such as in van den Berge’s original study (13). However, avoidance of hypoglycemia is probably more important than maintaining a blood sugar below a certain level.

The rush to publish guidelines creating a standard of care of intensive regulatory control of glucose in the ICU seems irrational in retrospect and demonstrates a potentially continued threat to patient safety. In addition, these guidelines increased the workload of both nurses and clinicians. Although often thought to

be revenue neutral, these mandates come at the price of increasing personnel costs both in implementation and monitoring of a guideline. Since personnel costs account for about 60-70% of the total costs in most health care systems, such mandates may be quite costly, or as the mandate for intensive glucose regulation illustrate, may actually be harmful. If the increase in mortality of 14% with intense glucose control is true as in the NICE SUGAR trial, this would calculate to one excess death for every 84 patients treated with this protocol (24,30). It seems unlikely that any ICU guidelines mandated in the future could compensate for the excess deaths caused by the mandated implementation of intense control of glucose. Fortunately, it is doubtful that implementation was 100%.

In an editorial entitled "Intensive insulin therapy in critical illness: when is the evidence enough?" Angus and Abraham (18) addressed the issue of when there is sufficient evidence for a concept to be widely applied as a guideline. Comparing the evaluation of intensive control of glucose in the ICU to evaluation of novel pharmacologic therapies, they point out that promising phase II studies are insufficient for regulatory approval. Instead, one, and usually two, large multicenter phase III trials are necessary to confirm reliability. The same principle is echoed in evidence-based medicine, where grade A recommendations are based on two or more large, positive, randomized, and multicenter trials. This seems a reasonable suggestion. Strong recommendations of this clinical importance should only be made when two or more large randomized controlled trials concur. However, it also seems unlikely that a mere review article such as this or the multiple recommendations from clinicians such as occurred with intensive control of glucose in the ICU will attenuate the exuberance of regulatory agents to mandate physicians and nurses to conform to their guidelines. Perhaps what is needed is an independent Federal or private agency to review and approve guidelines, and as Angus and Abraham suggest require at least two randomized, multicenter trials before implementation. As long as regulatory agencies accept no responsibility for harmful recommendations, it seems likely that in the absence of regulation, mistakes similar to the mandate to intensively regulate glucose in the ICU are likely to reoccur.

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