PERIOPERATIVE GLUCOSE CONTROL AND CARDIOVASCULAR COMPLICATIONS OF THE CARDIAC PATIENT

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INTRODUCTION

Unless a cure is found, the number of patients suffering from diabetes mellitus (OM) and its co-morbidities will continue to rise. According to the World Health Organization, a diabetes epidemic is already underway. In 1985, an estimated 30 million people worldwide suffered from diabetes. By 2000 that number reached 177 million. By 2025, researchers project that DM will affect roughly 300 million people and result in approximately 4 million deaths per year, many from cardiovascular complications.[1]

According to Boyle et al., the number of Americans who are diagnosed with DM is projected to increase 165%, from 11 million in 2000 to 29 million in 2050.[2]

An increasing number of diabetic patients are presenting for anesthesia and surgery, which may translate to greater numbers of surgical patients at risk for ischemic heart disease. While OM has long been considered to be a significant predictor of perioperative cardiovascular morbidity and mortality, recent studies indicate that hyperglycemia, rather than diabetes, is responsible for adverse clinical outcomes. These studies imply that hyperglycemia is an independent predictor of perioperative cardiovascular risk, and that aggressive treatment of hyperglycemia may significantly decrease complications of myocardial ischemia and infarction.

THE LINK BETWEEN HYPERGLYCEMIA AND CARDIOVASCULAR COMPLICATIONS

In one study,[3] the odds ratio for sustaining an acuce MI increased to 1.5, 3.4 and 6.0 at fasting blood glucose concentrations of approximately 90, 110 and greater than 115 mg/di, respectively {Table 1).

In a meta-analysis of 20 studies involving more than 95,000 patiems, there was a direct relationship benveen fasting and postprandial blood glucose concentration and the risk of a cardiovascular event such as sudden cardiac death, acute myocardial infarction (AMI) or a cerebrovascular accidem. This relationship was apparem even for glucose levels below the usual diabetic threshold, since the glucose cur off for diabetes {fasting of 126 mg/di and post-glucose load value of 200 mg/di) was chosen ro identify individuals at risk for eye and kidney disease without regard ro the risk of cardiovascular disease.[4]

Another study of 1,826 critically ill patients found a similar relationship between hyperglyc emia and mortality. The mortality rate for patients with glucose levels of 100-119 mg/di was 27%, while chat for patients with glucose levels of 80-99 mg/di was 9% - although the range of both of these values were still within normal limits for chat facility. In addition, mean and maximum glucose levels were significantly higher among non-survivors than among survivors for the entire group of patients.[5]

In a study of 1,548 critically ill patients admitted in a surgical ICU, the group chat received aggressive therapy - that is, insulin infusion ro maintain blood glucose levels below 110 mg/di - had an ICU mortality of only 4.6% compared ro 8% for rhe traditionally created group, in which insulin infusion was started only if the glucose level exceeded 215 mg/dl. Overall in-hospital mortality of the aggressively treated group was reduced by 34%. The lower mortality and morbidity seen in chis group was not related ro whether or nor the patient had diabetes (13% of patiems) or if their surgery prior ro admission to the ICU was cardiac (60% of patients).[6] Two additional studies in critically ill patients suggest char the lowered glucose level, rather than

Hyperglycemia: Independent Predictor Of CV Risk	
Fasting Blood Glucose	**Odds ratio for Acute MI**
90	1.5
110	3.4
>115 mg/di	6

Table 1.. Adapted from: Kersten JR, Toller WG, Gross ER, Pagel PS, Warltier DC. Diabetes abolishes ischemic preconditioning: Role of glucose, insulin, and osmolality. Am J Physiol Heart Gire Physiol. 2000; 278:H1218-4.

Digami Trial: Prognostic Significance Of Hyperglycemia In T.1 +t.2 Diabetic Pts With Ami	
[Blood Glucose] On Admission:	LT. Mortality In Conv/y Treated Pts:
235	35%
235-298	40%
> 298 mg/di	55%

Figure 2. Adapted from Malmberg K. Norhammar A, Wedel H, Ryden L. Glycometabolic state at admission: important risk marker of mortality in conventionally treated patients with diabetes mellitus and acute myocardial infarction: long-term results from the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction(DIGAMI) study. Circulation. 1999;99:2626-32.

the dose of insulin administered, was responsible for reduced morralicy and morbidity. In the first study,7 glucose levels of 145 mg/dl were thought to be che critical value, above which worse outcomes were observed; in the other study, the critical value was only 110 mg/dl.,8

In che Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) trial, the prognostic significance of hyperglycemia was studied in 620 patients with type I and 2 diabetes who were admitted with AMI. It was shown that intensive insulin treatment initiated within hours of admission decreased long-term mortalicy. By comparison, there was a near linear relationship between admission glucose levels and morralicy when using a conventional, less aggressive approach to hyperglycemia (Table 2). The data suggested that right glucose control with insulin at least partially improved the adverse outcomes expected in patients presenting with hyperglycemia.'>

CONTROLLING HYPERGLYCEMIA IN PATIENTS WITH ISCHEMIC HEART DISEASE

When che heart muscle is exposed co a few brief periods (3-5 minutes) of ischemia, it develops the abilicy to protect itself against injury caused from more prolonged episodes of ischemia and reperfusion. This phenomenon is called myocardial (or ischemic) preconditioning. lschemic preconditioning reduces the size of infarcts, protects the heart against post-infarccion left ventricular dysfunction, improves functional recovery and protects from ventricular arrhyrhmias.[10-15] Anesthetic preconditioning can provide similar protective effects when che hearc has been previously exposed to inhalacional anesthetics. Patients with coronary artery disease (CAD) undergoing noncardiac or cardiac surgery commonly experience episodes of perioperative ischemia. Studies with animals have shown a linear relationship between the level of hyperglycemia and che severity of myocardial infarction as ref1ecred by myocardial infarct size. Also, hyperglycemia has been shown co atcenuace che cardioprocective effects of both ischemic and anesthecic precondirioning.[3-16]

In a study of 3,554 diabetic patients undergoing coronary artery bypass grafting (CABG), hyperglycemia was treated wich either intravenous or subcutaneous insulin. The patients treated with a continuous infusion of insulin had better glucose control (177 mg/di ±30 vs. 213 mg/di ± 41) and significantly lower mortality (2.5% vs. 5.3). le was concluded chat OM was a risk factor for morcaliry following CABG, and a multivariate analysis revealed char continuous insulin infusion was an independenc procective factor from dearh.'7

In another study, 141 patients undergoing CABG were prospectively randomized between rwo glycemic control regiments chat started prior to anesthesia and continued for 12 hours postoperatively. The first group had tight glucose control, with levels maintained between 125-200 mg/di using a continuous infusion of a glucose insulin pocassium solucion (GIK). The other group had standard therapy in which the glucose level was maintained below 250 mg/dl with imermitcenc subcutaneous injections of insulin. Ac 30 days pose-op, there was no monalicy observed in either group. However, chose patients in the GIK group had higher cardiac indices, reduced requirement for pacing and inotropic support, and lower incidence of atrial fibrillation, pneumonia and wound infection. Long-term follow up revealed only one death in the GIK group compared co six cardiovascular-related deachs in the non-GIK group. Those in the GIK group also had fewer episodes of ischemia and a lower angina class.[18]

The above data combined with information from additional studies[19,20] leads to the conclusion that in patients with CAD, there is a strong correlation between glucose levels and perioperative mortalicy and morbidity relaced co che severity of rhe ischemic episodes and myocardial infarction. Since the anesthesiologist's role is to prevent adverse outcomes, ir seems that controlling glucose levels can help achieve this goal, especially in patients with ischemic heart disease.

The Portland Diabetic Project, which studied 4,864 diabetic patients undergoing open heart surgery, showed the advers relacionship between perioperative hyperglycemia and cardiac surgery outcomes. It also elucidated rhe protective effects of intravenous insulin therapy in reducing adverse outcomes, as increasing hyperglycemia was found co be independently predictive of increased morraliry, deep sternal wound infection (DSWI) and longer length of stay. The application of the

Portland Continuous Insulin Infusion (CII) Protocol, with pre- and incraoperacive eight control of glucose below 150 mg/di and often between 70-110 mg/di followed by three days of CII, was also found to independently reduce the cardiac bypass-related risk of death and DSWI by 57% and 66% respectively-dropping it co the normal range for non-diabetics.[21]

Another study involving 1,579 diabetic and 4,701 non-diabetic patients undergoing cardiac surgery found a high glucose level during cardiopulmonary bypass to be an independent risk factor for death and morbidity for both patient groups. This further suggests that it is the intraoperative hyperglycemia and not the actual diabetes that pucs these patients at a higher risk for death and complications.[22] In a prospective study of 200 diabetic patients undergoing cardiopulmonary bypass surgery, poor intraoperacive glucose control (blood glucose concentration greater then 200 mg/di in four consecutive measurements despite insulin therapy) resulted in higher morbidity and signiftcanrly higher mortality (11.4% vs. 2.4%).23

The mean incraoperative glucose concentration in 409 patients undergoing cardiac surgery was evaluated against adverse outcomes developed 30 days poscoperacively. Adverse outcomes included death and other cardiac (new onset atrial fibrillation, heart block, cardiac arrest), and non-cardiac (infection, neurologic, renal, pulmonary) complications. Intraoperative hyperglycemia was again found to be an independent risk factor for post-operative complications including death. Additionally, a 20 mg/di increase in the mean intraoperative glucose level was associated with a more than 30% increase in mortality and morbidity.[24]

CONCLUSIONS

It is well established that critically ill diabetic patients suffering from medical or surgical conditions have higher cardiovascular-related mortality and morbidity and worse outcomes than non-diabetics. It is also common knowledge chat diabetic patients presenting for both cardiac and non-cardiac surgery have higher perioperative mortality and morbidity rares than non-diabetic patients. Recent studies, however, have revealed that hyperglycemic non-diabetic patients experienced negative outcomes similar co those of diabetic patients. This has lead co the theory that perhaps hyperglycemia and not diabetes may be responsible for these worse ouccomes, and char better perioperarive glucose control with continuous insulin infusions could improve overall resulrs.

This relatively new concept has been supported by several recent studies, most of which are retrospective. Furthermore, glucose level differences, even below the diabetic threshold and within the normal limits of most laboratories, have shown variations in outcome, with lower glucose levels yielding better outcomes in general. However, more prospective, randomized, controlled, double-blinded studies are needed to prove beyond any doubt char extremely tight glycemic control in the perioperative setting can modify a significant independent predictor of perioperative mortality and morbidity.

Anesthesiologists and other perioperarive specialists have a powerful weapon available co chem that can dramatically improve ouccomes. It is mandatory to develop and test a protocol for tight glucose control with continuous intravenous infusion of insulin throughout the preoperative period. The Portland protocol, or a similar one chat could become widely accepted and easy to use, can assist in reaching chis goal. In addition, strict guidelines must be established for hyperglycemic patients who present for elective surgery to determine whether or not the surgery can proceed safely or must be postponed until improved glucose control is achieved.

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