

In light of the increasing demand to establish protocols for glucose and insulin management, we are creating a departmental policy that allows each anesthesiologist the ability to determine what treatment is best for each patient in a particular clinical scenario.

1. There are very few, if any, data demonstrating that ‘tight’ (serum glucose 80-110 mg/dl) glucose control **during the operative procedure**, is of clear benefit.
2. It is still not clear if patients who **might** benefit from insulin infusions during acute (operative) settings, benefit from ‘tight’ glucose control or from having adequate insulin levels to aid in transcellular transport of nutrients and electrolytes.
3. There **are** data demonstrating a 10-40% incidence of significant hypoglycemia (<60 mg/dl) when ‘tight’ glucose control is attempted. Along with this is the potential for profound derangement in serum electrolyte (Potassium, magnesium) levels. We have experienced such cases in which subsequent reductions in serum potassium occur and are associated with increased ventricular ectopy.
4. For specific case scenarios there may be greater benefit in greater control for patients. These may include **certain neurosurgical cases**, or patients requiring **deep hypothermic circulatory arrest (DHCA)**. Another group of patients would include those with suspected and/or diagnosed **diabetic ketoacidosis (DKA)** for which aggressive hydration and insulin therapy are warranted.
5. For critically ill patients with significant **insulin resistance**, ‘tight’ glucose control will be very difficult, and attempts to do so may subsequently result in complications.

Review

The following is a review of the available literature followed by a suggested treatment policy:

Glucose homeostasis and control during the peri-operative period have received much attention due to a number of investigations associating hyperglycemia with adverse outcome. The literature is generated from either general medical patients receiving chronic insulin therapy, cardiac surgical patients, or critically ill patients. These data do not necessarily apply to all surgical patients. There a paucity of information about glucose management in a variety of surgical patients with diabetes and aggressive insulin therapy may result in dangerous hypoglycemia (< 60 mg/dl) (1,2).

Issues surrounding management of hyperglycemia include the following:

1. definition of hyperglycemia
2. etiology of peri-operative hyperglycemia
3. clinical importance and impact of acute (<24 hours duration) hyperglycemia
4. outcome differences between non-diabetics, type I diabetics, type II insulin requiring diabetics, and type II non-insulin requiring diabetics.

Perhaps with the exception of insulin requiring diabetics, the literature is not consistent regarding the need for or benefit of serum glucose control for surgical patients (2,3,4,5). A number of methodological issues complicate formation of definitive approaches toward monitoring and treatment of serum glucose during the peri-operative period. These issues include the inclusion criteria (diabetics (IDDM vs. NIDDM) vs. non diabetics), assessment and definition of hyperglycemia, and the varied insulin protocols employed.

The definition of perioperative hyperglycemia varies from > 110 mg/dl to as high as > 200 mg/dl measured recorded one time, four successive times, or as an average of a predetermined time period (hours to one day). One study even compared outcomes of cardiac surgical patients based on a peak intraoperative glucose of > < 350 mg/dl. Few of the studies report the presence or absence of variables (Table 1) contributing to increased serum glucose levels. Reported endpoints include hospital costs, ICU and hospital stays, infection, neuropathy, various end-organ dysfunction, and mortality.

Table 1: Variables contributing to perioperative hyperglycemia include:

Diabetic patients
Previously unknown diabetic patients
Feeding Regimens
Stress Response (Catecholamines; Glucagon, Cortisol)
Acute Illness
Surgery
Administration of Glucose or Steroids
Insulin Resistance or Withholding of Insulin
Inotropic/Vasoactive Medications

Insulin protocols range in bolus size and infusion rate directed at achieving different levels of serum glucose (**see protocols below**). These protocols are generated from cardiac surgical patients and critically ill patients, populations known for their perioperative insulin resistance and variable absorption of insulin. These protocols often include larger bolus doses and infusion rates and, therefore, may not be safely applied to the general surgical population.

Reported outcomes relating to hyperglycemia include adverse cardiac events, new infections, and death. Other outcomes include increased ICU and hospital stays, resource allocation, successful control of serum glucose, and hospital costs (**3,5**). Although several studies report lower initial postoperative serum glucoses (translated as improved postoperative control) for patients having had more aggressive glucose lowering management during surgery, outcomes were not consistently improved based on acute intraoperative therapies (**2,3,5**).

The discussion below refers to data generated from cardiac surgical patients or patients managed in an intensive care unit, both of which are at increased risk for morbidity and mortality due to variables not necessarily caused by or related to acute changes in serum glucose levels. Instead these variables, listed in **Table 1**, contribute to hyperglycemia, making this laboratory abnormality a marker of a sicker patient as opposed to a direct cause of acute morbidity. Whether or not these data can be extrapolated and applied to the general surgical population has not been demonstrated. Furthermore, the only data that directly apply to intraoperative management, suggest that early ICU glucose homeostasis is improved without other outcome benefit. (**3,14**)

A significant study included more than 1500 patients admitted to a surgical intensive care unit who required mechanical ventilation (reasons not included), the majority (>60%) of which included cardiac surgical patients (**5**). On arrival to the ICU (i.e. not intra-operative) patients were randomized to either receive 'intensive insulin management' to achieve a serum glucose between 80 and 100 mg/dl, or 'conventional management' to maintain serum glucose < 200 mg/dl. Upon discharge from the ICU all patients were then treated with conventional management. At baseline, the two groups of patients appeared to be comparable, based on APACHE II scoring. ICU management was compared using another scoring system (TISS-28), which showed both groups to be similar. As expected, glucose levels were lower and insulin therapy was greater in the study population. Although mortality, infection, and neuropathy (all transient) were improved in the study group, differences were only significant for non-cardiac surgical patients who were in the ICU for more than 5 days. Furthermore, the greatest reduction in mortality was found in patients with prolonged ICU stay, multi-organ failure with sepsis and a known septic focus. Documented hyperglycemia on admission was not associated with any adverse outcome. The authors concluded that intensive control of serum glucose improved outcomes in a selected patient population. Furthermore, they are only able to speculate that outcome was related to serum glucose levels as opposed to greater insulin administration and serum levels of insulin. These findings did not apply to the general surgical population..

Overall, the available data report an association between hyperglycemia and adverse outcome (5,6,7). This association is questionable at best if only intraoperative data are considered. Definitive data supporting 'tight' (80-120 mg/dl) glucose control during the perioperative period are lacking. However, opinion, does suggest a reduction in serum glucose levels to < 200 mg/dl for type I and/or insulin dependent diabetics during the intraoperative and immediate postoperative period (4).

Differentiating between insulin resistance and hypo-insulinemia is important when reviewing the literature (8-12). Cardiac surgical patients requiring cardiopulmonary bypass, have significantly elevated glucose levels despite a 374% increase in insulin levels (11). Postoperative glucose levels were higher for patients having been managed with systemic hypothermia (11).

The literature is, at best, mixed regarding outcome analyses and serum glucose control. Estrada et al reported no association between death, or infection for each 50 mg/dl serum glucose greater than 120 mg/dl (3). Hyperglycemia was associated with greater hospital costs and resource utilization. Diabetic patients incurred greater charges than non-diabetic patients due to drug administration, laboratory utilization, and increased ICU and hospital days.

Further confusion regarding the benefits of glucose control come from studies reporting benefits of GIK infusions (glucose-insulin-potassium). Despite the presence of hyperglycemia (approx. 250 mg/dl), patients receiving GIK required less cardiac support, had less cardiac injury, and fewer arrhythmias. Glucose levels were significantly higher in the GIK group when compared to the control group (12,13).

A reduction in sternal infections (2.3% to < 1%) in cardiac surgical patients was reported after institution of a rigid peri-operative insulin protocol to reduce peri-operative serum glucose levels to less than 130 mg/dl (14). However, at best, only 75% of patients reached target glucose goals defined by glucose levels in the ICU. Furthermore, it is not known how many blood glucose levels were measured during the peri-operative period, or how many were elevated before finally achieving a 'controlled' condition. There was no statistical association between glucose control and a reduced rate of infection, nor was the reduction in infection reported to be statistically significant. Furthermore, during this time clinicians also changed or instituted several other procedures to prevent infection. These included alterations in scrub technique, changes in surgical prepping and draping, changes in antibiotic prophylaxis, and presence of attending surgeon at the start of the surgical procedure. Although, improved control of perioperative glucose was reported in up to 75% of targeted patients, it is not evident that this resulted in improvement in outcome.

Profound hypoglycemia (glucose < 60 mg/dl) for patients, in which aggressive intra-operative control of serum glucose was attempted, has been reported (1). Despite aggressive insulin administration in the study group, serum glucoses recorded during CPB were similarly > 250 mg/dl in both the study and control group. For the study group a 40% incidence was reported on arrival to the ICU.

Quattara et al studied the impact of glucose levels (<180 mg/dl in OR and < 140 mg/dl in ICU) for 200 diabetics after cardiac surgery requiring CPB (15). Poor glucose control was associated with increased morbidity. However patients with greater morbidity had significantly greater risk factors (reduced LVEF, history of arrhythmias, pulmonary hypertension, chronic renal insufficiency, more complicated surgical procedures, greater CPB times, and higher Euroscores) most of which were independent risk factors for outcome.

Kubal et al compared non-insulin vs. insulin dependent diabetics undergoing cardiac surgical procedures. Both were then compared to non-diabetics (16). The authors were not able to demonstrate a difference in outcome between non-IDDM and non-diabetics, however patients with IDDM had a greater mortality. Diabetic patients possessed greater risk factors than non-diabetics. IDDM was associated with greater renal failure, and sternal wound infection. However, when diabetics were matched to non-diabetics using a propensity score analysis, outcome was similar. Although the authors did not study glucose control, they associated systemic outcome with the presence of diabetes and surmised that systemic control of serum glucose would reduce adverse outcome.

For non-diabetics, **Butterworth et al**, were not able to demonstrate an improved neurologic outcome, using a battery of tests, with tight glucose control (2). However a greater incidence of hypoglycemia (<70 mg/dl) was also reported in the study group.

Finney et al reported data that can be interpreted to either demonstrate a benefit of tight glucose control or show that sicker patients have higher serum glucose levels and require greater administration of insulin (6). **Finney et al** studied 531 patients in a medical/surgical intensive care unit. The authors administered insulin to maintain glucose between 90 and 145 mg/dl. Lower glucose levels were associated with trends (p=ns) toward reduced mortality. In addition, greater administration of insulin was associated with increased mortality. The authors concluded that tighter control of serum glucose resulted in improved outcome. However, the association between greater insulin administration and mortality suggest that insulin resistance was associated with both poor glucose control and greater mortality. In other words, sicker patients have greater insulin resistance and higher glucose levels despite receiving greater amounts of insulin. Glucose levels in less complicated patients are easier to control.

Supportive data for glucose control (<140 mg/dl) was reported in a meta-analysis of 26 studies evaluating survivors of stroke (17). Details of management, ability to control serum glucose, and causes of death and co-morbidities are not included, however, the authors report an, overall, improved outcome with glucose control. Previously, the authors previously had reported that stress hyperglycemia was associated with greater mortality and myocardial infarction (7). In vitro data showed improved phagocytic activity when inflammatory cells were placed in an insulin bath, however, there was no relation to specific serum glucose levels (18). Finally, **Srinivassan et al** reported acute improvement in myocardial perfusion reserve during administration of insulin and reduced glucose levels (HE) compared to a group to which insulin was administered, however glucose levels remained elevated (HH) (19). It should be noted, however, that

in the HH group, insulin levels had declined to levels below that of the HE group and may have impacted on the results. Nevertheless, the authors reported that both insulin administration and serum glucose control (5-7 mmol/L vs 11-14 mmol/L) improved myocardial blood flow during stress periods. Other data support the benefit of insulin on coronary flow (20).

All data considered, there is little evidence that support acute benefits of tight glucose control during the immediate peri-operative period for any type of patient undergoing surgery. Any suggestion otherwise, would be based on the extrapolation of data from studies involving critically ill patients in the ICU for a number of days or from other postoperative data likely involving cardiac surgical patients. Furthermore, these data do not distinguish between stress hyperglycemia and insulin resistance (i.e. a sicker patient), and hypo-insulinemia. Alternatively, the administration of insulin alone may have benefit without having to achieve ‘tight control’. Current guidelines regarding cardiac surgical patients recommend controlling blood glucose below 200 mg/dl for diabetic patients (more so insulin dependent diabetic patients). Therefore, the following recommendations can be proposed for the intraoperative and immediate (24 hours) care of the surgical patient:

Insulin Locations:

Regular insulin can be found in the following Pyxis locations:

- PACU
- Bridge (clean core)
- Davol (by front desk)
- Rooms 9/10 connector
- Rooms 18/19 connector

Currently, there are 5 multipurpose syringe pumps that can be found in either the Davol Anesthesia workroom, or in rooms 9 and 10.

Regular insulin can be mixed in saline in a concentration determined by the anesthesia team.

Insulin Preparations: Onset, peak effect, and duration are listed in hours unless otherwise written.

	Onset (Hours)	Peak Effect (Hours)	Duration (Hours)
Short-acting (IV)	5 minutes	10-20 minutes	30-45 minutes
Short-acting (SC)			
Crystalline	1	2-4	6-8
Semilente	1.5	5-7	12-18
Intermediate (SC)			
NPH	1-2	10-20	20-24
Lente	1-2	14-18	20-24
Prolonged (SC)			
Protamine	6-8	16-24	24-36
Ultralente	6-8	22-26	24-36

IV= intravenous; SC= subcutaneous

Guidelines

Insulin-dependent diabetics:

For outpatient surgical procedures:

AM case:

- a. No long or intermediate insulin the AM of surgery.
- b. Blood glucose determination in the AM in holding unit.
- c. Intra- and post-operative monitoring of blood glucose levels at discretion of attending anesthesiologist.

PM case:

- a. ½ dose intermediate-acting insulin on arrival to hospital or in preop area.
- b. Blood glucose determination in the holding unit.
- c. Intra- and post-operative monitoring of blood glucose levels at discretion of attending anesthesiologist.

For Same Day Admit (SDA) Patients:

Hold All AM Long-Acting Insulin Preparations

AM case:

- a. ½ dose intermediate-acting insulin on arrival to hospital or in preop area.
- b. Blood glucose determination in the AM in holding unit.
- c. Intra- and post-operative monitoring of blood glucose levels at discretion of attending anesthesiologist.
- d. Aim to keep blood glucose levels >80mg/dl and <250mg/dl at the discretion of the attending anesthesiologist.

PM case:

- a. ½ dose intermediate-acting insulin on arrival to hospital or in preop area.
- b. Blood glucose determination in the holding unit.
- c. Intra- and post-operative monitoring of blood glucose levels at discretion of attending anesthesiologist.
- d. Aim to keep blood glucose levels >80mg/dl and <250mg/dl at the discretion of the attending anesthesiologist.

For In-House Patients:

Preoperative management can be the same as SDA patients if intermediate duration insulin has been previously ordered and listed on the ‘regular floor orders’. Otherwise, preoperative insulin management could follow a sliding scale written in the regular orders.

Insulin Pumps:

The specific information regarding the infusion rates for these pumps should be obtained from either the primary care physician or, preferably, the patients endocrinologist. As there is little data regarding the intraoperative management for these special cases, the infusion rate can either be left un-

altered, or perhaps halved during the pre- and intra-operative (NPO) period. These cases should be assessed on a case-by-case basis in conjunction with the PCP or endocrinologist.

Non-insulin-dependent diabetics:

Hold oral hypoglycemic medications.

Monitoring of blood glucose will be at the discretion of the attending anesthesiologist based on anticipated length and complexity of the surgical procedure.

Non diabetics:

In the absence of **Special Case Scenarios** (listed below), there is little data demonstrating any benefit for intraoperative glucose monitoring, nor for a need for insulin therapy. Any insulin/glucose management or glucose monitoring would be at the discretion of the attending anesthesiologist.

Specific Case Scenarios:

- a. Neurosurgical patients at increased risk for sustained intraoperative brain ischemia (e.g. craniotomy for intracranial aneurysm or severe closed head trauma) or who are receiving high dose steroids for spinal cord injury.
- b. Cardiac surgical patients requiring Deep Hypothermic Circulatory Arrest
- c. Intensive-care-unit patients with a previously written insulin regimen

For these Special cases, tighter insulin/glucose management and monitoring may be warranted. Determination of which would be at the discretion of the attending anesthesiologist.

For patients receiving insulin infusions, blood sugar monitoring is recommended.

Additional metabolic monitors may include:

Serum Potassium

Serum Magnesium

Arterial Blood Gas Analysis

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