Inpatient Glycemic Management

Shashank R Joshi

INTRODUCTION

Recently, there has been a heightened interest in improving the quality and safety of the management of diabetes and hyperglycemia in the hospital. While observational data strongly suggest an association of hyperglycemia with morbidity and mortality in adults on general medical and surgery units, research has still not defined the best practices for managing hyperglycemia in the hospital outside the ICU, and today there is the best course for management for the patient in the ICU is unclear. As a consequence, many physicians and inpatient hospital set-ups including ICUs do not have a well-formulated approach to managing hyperglycemia in either the non-critically ill or the critically ill hospitalized patient, and the use of insulin therapy to attain targeted blood glucose (BG) control is often subject to practice variability, leading to suboptimal or even adverse glycemic outcomes. The current “guidelines” for the management based on understanding of glucose physiology, insulin pharmacodynamics, the characteristics of currently available insulin preparations and scant Randomised clinical trial experience. The change which has now started is based on several randomized controlled trials which have demonstrated that hospitalized type 2 diabetes patients experienced better glycemic control when treated with a physiologic insulin regimen than when treated with sliding scale insulin alone. These guidelines had also extended to the ICU, but the initial excitement that tight control of glucose levels in the ICU setting would decrease morbidity and mortality (based on Vandenberg SICU Belgian data) has been tempered by more recent studies (Aus-NZ NICE Sugar and Vandberg’s MICU data) that have not duplicated these results. Modern inpatient diabetes protocols have been successfully employed to manage diabetic patients who are not eating and have implemented strategies to manage hypoglycemia. Yet in vast majority of cases inpatient management remains a neglected area. The current evidence and tip to improve inpatient diabetes management in hospitals for better outcomes will be discussed.

Factors Influencing Glycemic Control In Hospitalized Patients

The major factors that need to be overcome in order to achieve glycemic control in the hospitalized diabetic patient are discussed in Table I.

Table I. Factors which Alter Glycemic Control In Hospital

- Increased counterregulatory hormones: in the perioperative period with increased insulin resistance due to increased catecholamines, cortisol, growth hormone and glucagon
- Unpredictable eating: From illness, NBM for tests, Changing meal times
- Changing IV glucose rates
- Unusual timing of insulin injections: Injection may be ordered on a timed basis, not having any relationship to meal or insulin often given after meal is eaten
- Use of medications such as glucocorticoids and catecholamines
- Lack of exercise
High ICU Blood Glucose and Adverse Cardiovascular outcomes

Numerous epidemiological and retrospective studies show diabetes increases morbidity and mortality for myocardial infarction, coronary bypass surgery as well as stroke- acute cerebral ischemia. There has been a two to four fold rise in the mortality risk in patients admitted with a stroke. In an extensive retrospective review of 259,040 critically ill patients conducted by the Veterans Affairs Inpatient Evaluation Center based in Cincinnati, for all patients reviewed, hyperglycemia was an independent predictor of mortality starting at 111 mg/dl. However, in diabetes patients, the increase in mortality risk was not seen until mean glucose was >146 mg/dl. Moreover, there were distinct differences in the association of hyperglycemia and mortality depending on the underlying diagnosis. The correlation was most significant for acute myocardial infarction (1.7-6 fold increase in predicted mortality), unstable angina (1.4 to 3 fold increase in predicted mortality), and stroke (1.8 to 29 fold increase in predicted mortality). A significant but weaker effect was seen in patients with sepsis, pneumonia, and pulmonary embolism. But hyperglycemia was not found to be associated with mortality in diseases such as COPD and hepatic failure, hip fractures. It is well known that hyperglycemia greater than 200 mg/dl leads to fluid and electrolyte abnormalities secondary to osmotic diuresis, decreased leucocyte function, delayed gastric emptying, increased surgical complications including risk for postoperative nosocomial infections increased by a factor of 5.7 when glucose >220 mg/dl. Odds ratio of wound infection increased to 1.17 with glucose >200 mg/dl and to 1.78-1.86 when glucose >253 mg/dl as well as delayed hospital discharge. The length of stay was compared for patients in “control” (glucose 60-250 mg/dl) and those with “fluctuating” glucose (glucose <60 or >250 mg/dl) (Table II).

Can Tight Glycemic Control Influence Cardiovascular Outcomes in ICCU?

The above data indicated that high glucose levels are associated with a poor outcomes. There is uncontrolled data showing that improving glycemic control improves outcomes in various parameters. There is an improved WBC function demonstrated by perioperative insulin infusion improves neutrophil phagocytic activity, and, in one study, led to a level at 75% of baseline activity compared to only 47% in a control group as well as decreased infections with perioperative intravenous insulin infusion designed to keep glucose <200 mg/dl reduces the risk of wound infection in diabetics after open heart operations. There is also data to show that incidence of deep wound infections decreased from 2.4 to 1.5% in one study and to 2.0 to 0.8% in another. The decreased postoperative mortality in CABG from Portland, USA is well known. Furnary and colleagues from Portland have administered IV insulin to their post-CABG diabetic patients with glucose goals decreasing from 150 mg/dl in around 2000 to now the low 100 mg/dl range. Their uncontrolled, retrospective analyses have shown decreased mortality with glucose under 150 mg/dl. Yet after DIGAMI-2 the decreased post-myocardial infarction morbidity and mortality remains conflicting and controversial. The DIGAMI-1 (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) study group treated perimyocardial infarction diabetic patients with IV insulin infusion and then algorithm based SQ premeal insulin (for one year) and the mortality at 1 year was 26% in the control patients compared to 19% in the study patients, mortality at 3.4 years was 44% in the control patients compared to 33% in the study patients. After this study, it was not clear if the benefit was due to the IV insulin, the prolonged SQ insulin, or another intervention. So a second study was performed which had a neutral outcome viz. DIGAMI 2. In DIGAMI 2, three treatment strategies were compared: group 1, acute insulin-glucose infusion followed by insulin-based long-term glucose control; group 2, insulin-glucose infusion followed by standard glucose control; and group 3, routine metabolic management according to local practice. There were no significant differences in morbidity expressed as non-fatal reinfarctions and strokes among the three groups. The DIGAMI 2 did not support the hypothesis that an acutely introduced, long-term insulin treatment improves survival in type 2 diabetic patients following myocardial infarction when compared with a conventional management at similar levels of glucose control or that insulin-based treatment lowers the number of non-fatal myocardial reinfarctions and strokes. However, an epidemiological analysis confirms

<table>
<thead>
<tr>
<th>Hospital Illness</th>
<th>Glycemic Control As per protocol</th>
<th>Brittle Glycemic Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Myocardial Infarction</td>
<td>4.1</td>
<td>6.7</td>
</tr>
<tr>
<td>CABG</td>
<td>6.3</td>
<td>8.2</td>
</tr>
<tr>
<td>Community Acquired Pneumonia</td>
<td>4.5</td>
<td>6.3</td>
</tr>
</tbody>
</table>

Table I. Length of Hospital Stay and Glycemic Control
that the glucose level is a strong, independent predictor of long-term mortality in this patient category, underlining that glycemic control seems to be an important part of their management.

**Does Tight Glycemic control decreased morbidity and mortality in critically ill patients?**

Vandenbergh et al from Surgical Intensive care from Belgium showed that Post-operative patients on ventilators: A comparison of patients with plasma glucoses between 80-110 mg/dl (intensive treatment), and those given insulin only if glucoses were >215 mg/dl and then maintained 180-200 mg/dl (control) indicate that: Intensive insulin treatment decreased overall mortality from the control rate of 8% to 4.6% (p=0.04). In addition, the intensive treatment decreased sepsis by 46%, need for dialysis by 41%, and these patients were less likely to require prolonged ventilatory support and intensive care. However, on critical review of this paper, there are questions regarding the generalizability of the data. The subjects received significantly more glucose daily than is usual care in the US. In addition, the benefit was mainly seen in the surgical patients who remained in the ICU for greater than 5 days, also a small percentage of patients. Finally, on secondary analysis, there was only a small difference between the long-term mortality outcomes between the group that had glucoses <110 mg/dl and the group that had glucoses 110-150 mg/dl. However the same group from their Medical ICU patients had a different result which indicated that intensive insulin therapy significantly reduced morbidity but not mortality among all patients in the medical ICU. Patients were preselected as having the potential to stay in the ICU for more than 3 days. In sub-analysis, the risk of subsequent death and disease was reduced in patients treated for three or more days, but these patients could not be identified before therapy. The VISEP study was a large multicenter, prospective comparison of intensive IV insulin treatment compared to less tight control which showed no benefit to the tighter glucose control and was stopped early due to increased risk of hypoglycemia. They concluded that these studies (this one and the Van den Berghe study above) establish that intensive insulin therapy has no measurable, consistent benefit in critically ill patients in a medical ICU, regardless of whether the patients have severe sepsis, and that such therapy increases the risk of hypoglycemic episodes. Then the NICE-SUGA a large multicenter randomized trial comparing the effects of intensive glucose control (target glucose 81-108 mg/dL) and conventional glucose control (target glucose < 180 mg/dL) on death from any cause within 90 days of randomization. 6104 patients were randomized, all adults admitted to the ICU in the 24 hours prior, and all expected to require treatment in the ICU for 3 or more days. More of those randomized to intensive control died than those randomized to conventional control (27.5% vs. 24.9%, p = 0.02), severe hypoglycemia was reported in more of those randomized to intensive control than to conventional control (6.8% vs. 0.5%, p < 0.001), and there was no significant difference in length of stay in the ICU, median days of mechanical ventilation, or renal-replacement therapy. The COITSS Study is a multicenter study of hydrocortisone-treated patients with septic shock, intensive insulin therapy did not improve outcomes. A recent meta-analysis identified 29 studies that included 8432 patients and reported 1869 deaths. The overall relative risk of death for those treated with tight glucose control was 0.93 (95% confidence interval, 0.85-1.03). Additionally, subgroup findings for trials that targeted a blood glucose concentration of less than 110 mg/dL and subgroups selected according to the type of ICU (surgical, medical, or medical-surgical) did not demonstrate a significant reduction in mortality.

**Intraoperative glucose management**

There has been very little attention to actual outcomes from intraoperative glucose control. An early retrospective analysis showed that lower glucoses during cardiovascular surgery were associated with improved outcomes. However, when tested with a randomized, prospective study, maintaining glucoses less than 110 mg/dL, there was no apparent benefit to intensive insulin therapy during cardiac surgery. It did not reduce perioperative death or morbidity. In fact, there was an increased incidence of death and stroke in the intensive treatment group (though not statistically significant) and raises concern about routine implementation of this intervention.

**Glycemic Goals for Inpatient Control**

The general goal for glycemic control is to avoid the undesirable short and long term effects of hypoglycemia and hyperglycemia. From a practical standpoint, this means that glucoses should be between 140 to 180 mg/dL. Glucose values below 180 mg/dL should decrease the short-term diabetes complications that may occur during a hospitalization, while lower glucoses (with a HgA1c goal of about 7%) are desired for the long-term prevention of microvascular and macrovascular disease. Hypoglycemia should be avoided to prevent counterregulatory hormone-induced cardiovascular complications. From the data discussed above, specifically the large retrospective ICU reviews, the actual benefit of
specific goals in patients with different underlying diagnoses remains unclear ADA and AACE targets 140-160 mg/dl and the data on 110-140 mg/dl is unclear and below 110 mg/dl may be harmful.

**General Medical and Surgical Wards**

At present, recommended glycemic targets for non-critically ill hospital patients are based entirely on expert opinion, as there have been no clinical studies directly comparing different glycemic targets in this patient population. However, the American College of Endocrinology, the American Association of Clinical Endocrinologists, and the American Diabetes Association do provide recommendations about glycemic targets for inpatients. Although controversial, these recommendations make it clear that uncontrolled hyperglycemia is no longer the accepted standard of care for hospitalized patients. Of note, most hospitals adopt glycemic targets that are less stringent than those advocated, recognizing the challenges of controlling blood glucose levels in hospitalized patients, and the potential risk for hypoglycemia when lower BG targets are used. Each hospital must have their own glycemic targets which are jointly decided by the endocrinologist, diabetologist, intensivist and nursing staff. In practice this range has been 110-140 mg/dl for the lower BG limit and 140-180 mg/dL for the upper BG limit. It is also important to note that the recommendations from professional organizations emphasize the need to individualize BG targets, based upon the clinical circumstances of each patient. In Lilvati Hospital we have our own protocol based on joint team training and avoidance of hypoglycemia based on the available evidence and guidelines.

**ICU**

The postoperative ICU and Medical ICU glycemic control trial data is discussed above demonstrates the controversy about the initial Vandenberg protocol that suggested goals of 80-110 mg/dl. Most global and Indian institutions based on present evidence supports maintaining glucose < 110-180 mg/dl with the avoidance of hypoglycemia. AACE and ADA have updated their recommendations and moved from a goal of 80-110 to now 140-180 mg/dl though 110 to 140 mg/dl may eventually evolve. Based on Current evidence, insulin infusion should be used to control hyperglycemia in the majority of critically ill patients in the ICU setting, with a starting threshold of no higher than 180 mg/dl. Once IV insulin therapy has been initiated, the glucose level should be maintained between 140 and 180 mg/dl with better benefit at the lower end of this range. Although strong evidence is lacking, somewhat lower glucose targets may be appropriate in selected patients targets <110 mg/dl like in SICU patients with parental nutrition but are not routinely recommended. Use of In house In patient insulin infusion protocols with demonstrated safety and efficacy, resulting in low rates of occurrence of hypoglycemia are often in current use.

**SUMMARY**

Recently, there has been a heightened interest in improving the quality and safety of the management of diabetes and hyperglycemia in the hospital. While observational data strongly suggest an association of hyperglycemia with morbidity and mortality in adults on general medical and surgery units, research has still not defined the best practices for managing hyperglycemia in the hospital outside the ICU, and even today there is no the best course for management for the patient in the ICU is unclear. As a consequence, many physicians and inpatient hospital set ups including ICUs do not have a well-formulated approach to managing hyperglycemia in either the non-critically ill or the critically ill hospitalized patient, and the use of insulin therapy to attain targeted blood glucose (BG) control is often subject to practice variability, leading to suboptimal or even adverse glycemic outcomes. The current “guidelines” for the management based on understanding of glucose physiology, insulin pharmacodynamics, the characteristics of currently available insulin preparations and scant randomised clinical trial experience. The change which has now started is based on several randomized controlled trials which have demonstrated that hospitalized type 2 diabetes patients experienced better glycemic control when treated with a physiologic insulin regimen than when treated with sliding scale insulin alone. These guidelines had also extended to the ICU, but the initial excitement that tight control of glucose levels in the ICU setting would decrease morbidity and mortality (based on Vandenberg SICU Belgian data) has been tempered by more recent studies (Aus-NZ NICE Sugar and Vandberg’s MICU data) that have not duplicated these results. Modern inpatient diabetes protocols have been successfully employed to manage diabetic patients who are not eating and have implemented strategies to manage hypoglycemia. Yet in vast majority of cases inpatient management remains a neglected area.
SELECTED READING
Website: www.aace.org In patient Glycemic Control Center

6. Simon Finfer; Anthony Delaney Tight Glycemic Control in Critically Ill Adults JAMA. 2008;300(8):963-965