Inpatient Management of Diabetes Mellitus

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Abstract

Inpatient hyperglycemia is associated with increased morbidity and mortality. The length of hospital stay and cost of care is higher for patients with diabetes than for others. Current evidence suggests that tight control of hyperglycemia in critically ill hospitalized patients with diabetes or acute hyperglycemia has been shown to reduce the risk of morbidity and mortality. In view of risk of severe hypoglycemia with near normal blood glucose target, latest consensus is to adopt a less stringent target of 140–180 mg/dl. The development of insulin analogs with more physiologic time-action profiles, improved insulin delivery systems, and standardized protocols for subcutaneous insulin administration and intravenous insulin infusion have improved the safety and convenience of insulin therapy for treating inpatients.

Hyperglycemia in Hospitalized Subjects

Hyperglycemia is very common in the inpatient setting. It is seen in patients with and without diabetes. Patients with type 1 or type 2 diabetes mellitus are frequently admitted to hospital, usually for the treatment of conditions other than the diabetes. The prevalence of diabetes rises with increasing age, as does the prevalence of other diseases; both factors increase the likelihood that an older person admitted to hospital will have diabetes. Glycemic control is unstable in these patients because of the stress of the illness or procedure, the concomitant changes in dietary intake and physical activity, and the frequent interruption of the patient’s usual antihyperglycemic regimen. Conditions like trauma, hemorrhage, burns, hypoxia, infections, sepsis, or shock, may induce both insulin resistance and relative insulin secretory defect. This leads to increased muscle protein degradation, decreased peripheral glucose disposal, lipolysis resulting in increased circulating nonesterified fatty acids, hyperlactatemia, and increased hepatic glucose output. Mechanisms of defects of insulin signaling and relative β-cell suppression seen during acute illness are still under evaluation.

Inpatient hyperglycemia is associated with increased morbidity and mortality. The length of hospital stay and cost of care are greater for patients with diabetes than for those without it. In addition, it results in additional health care costs due to extended hospital stay, readmission, or complications associated with hyperglycemia. However, still inpatient hyperglycemia is under-recognized, underreported, and suboptimally managed. To improve outcomes, proactive assessment of inpatients’ glycemic status and aggressive treatment approaches are needed.

Insulin Therapy for Inpatient Hyperglycemia: Evidence and Controversy

Improving hyperglycemia management in hospitalized patients provides an opportunity to reduce morbidity, mortality, and health care costs. Insulin is the most preferred glucose-lowering agent in this setting. Other antidiabetic drugs are not suitable in managing hospital hyperglycemia due to difficulty in titrating their dose to meet fluctuating blood glucose levels, associated co-morbid conditions like hepatic and renal impairment, and most importantly the need for quick achievement of target blood sugar levels.

Insulin exerts its protective action on several tissues and signaling pathways like the heart, the endothelium (vasodilatory

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>N</th>
<th>Outcome</th>
<th>Intervention</th>
<th>ARR</th>
<th>RRR</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIGAMI</td>
<td>CCU (AMI)</td>
<td>620</td>
<td>1-year mortality</td>
<td>IIP (D5W) + MDI: 126-196 mg/dl</td>
<td>7.5%†</td>
<td>29%</td>
</tr>
<tr>
<td>Furnary</td>
<td>CTICU</td>
<td>2467</td>
<td>Sternal infections</td>
<td>IIP: 150-200 mg/dL</td>
<td>1.2%</td>
<td>66%</td>
</tr>
<tr>
<td>Leuven</td>
<td>SICU</td>
<td>1548</td>
<td>ICU mortality</td>
<td>IIP: 80-110 mg/dL</td>
<td>3.4%</td>
<td>42%</td>
</tr>
<tr>
<td>Krinsley</td>
<td>ICU</td>
<td>1600</td>
<td>Hospital mortality</td>
<td>SC or IV insulin, &lt;140 mg/dL</td>
<td>6.1%</td>
<td>29%</td>
</tr>
<tr>
<td>Leuven</td>
<td>MICU</td>
<td>1200</td>
<td>Hospital mortality</td>
<td>IIP: 80-110 mg/dL</td>
<td>2.7%†</td>
<td>7%†</td>
</tr>
</tbody>
</table>

AMI, acute myocardial infarction; ARR, absolute risk reduction; CCU, coronary care unit; CTICU, cardiothoracic ICU; IIP, insulin infusion protocol; IV, intravenous; MDI, multiple insulin; MICU, medical ICU; RRR, relative risk reduction; SC, subcutaneous; SICU, surgical ICU.

Fig 2: Studies showing benefits of intensive glucose management in critical care
action, protection against vessel wall inflammatory processes), immune system, the inflammatory pathway, the coagulation pathway, etc. Protection may be conferred by insulin in part by metabolic controls as well as other direct or indirect nonmetabolic effects of insulin like nitric oxide–mediated improvement of endothelial function; regulation of nuclear factor-κB; inhibition of the production of harmful reactive oxygen species; regulation of the transcription of proinflammatory genes, adhesion molecules, and chemokines; and suppression of early growth response gene-1, plasminogen activator inhibitor 1, and matrix metalloproteinases.

van den Berghes and colleagues conducted a landmark study to evaluate the benefits of intensive insulin therapy in critically ill patients. It was a prospective, randomized, controlled study involving adults admitted to surgical intensive care unit who were receiving mechanical ventilation. On admission, 1548 patients were randomly assigned to receive intensive insulin therapy (maintenance of blood glucose at a level between 80 and 110 mg per deciliter) or conventional treatment (infusion of insulin only if the blood glucose level exceeded 215 mg per deciliter) and maintenance of glucose at a level between 180 and 200 mg per deciliter. Intensive insulin therapy reduced mortality during intensive care from 8.0% with conventional treatment to 4.6% (P < 0.04, with adjustment for sequential analyses). 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 5 days (20.2% with conventional treatment, vs. 10.6% with intensive insulin therapy; P = 0.005). Intensive insulin therapy also reduced overall in-hospital mortality by 34%, bloodstream infections by 46%, acute renal failure requiring dialysis or hemofiltration by 41%, the median number of red-cell transfusions by 50%, and critical-illness polyneuropathy by 44%, and patients receiving intensive therapy were less likely to require prolonged mechanical ventilation and intensive care. Following this, several studies have published supporting as well as refuting the results of this study.

Subsequent to the initial van den Berghes study, some multicenter trials including the latest NICE SUGAR study have shown an increased frequency of hypoglycemia and have failed to consistently demonstrate improved outcomes with intensive insulin therapy. In the NICE SUGAR study, 6104 critically ill patients were randomized to undergo either intensive glucose control, with a target blood glucose range of 81–108 mg per deciliter, or conventional glucose control, with a target of 180 mg or less per deciliter. The primary end point was death from any cause within 90 days after randomization. A total of 829 patients (27.5%) in the intensive-control group and 751 (24.9%) in the conventional-control group died. Severe hypoglycemia (blood glucose level ≤40 mg per deciliter) was reported in 6.8% in the intensive control group and 0.5% in the conventional-control group (P < 0.001). This study concluded that a blood glucose target of 180 mg or less per deciliter resulted in lower mortality than did a target of 81 to 108 mg per deciliter.

Hospitals and expert panels are in the process of examining the combined evidence and considering modifying treatment goals. Current strategy is continued focus on avoiding hyperglycemia with less aggressive glycemic targets in the critically ill and rational subcutaneous insulin in the noncritically ill, avoiding a return to the non-physiological sliding-scale insulin. The latest consensus statement from AACE/ADA on inpatient management of hyperglycemia is a welcome step in this regard.

Current Consensus on Inpatient Blood Glucose Management

Evidence from several cohort studies and randomized controlled trials showing improved hospital outcomes with intensive treatment of hyperglycemia led the American College of Endocrinology (ACE) and the American Association of Clinical Endocrinologists (AACE), in collaboration with the American Diabetes Association (ADA) and other medical organizations, to develop recommendations for treatment of inpatient hyperglycemia in 2004. The latest consensus statement from AACE/ADA on inpatient management of hyperglycemia released in 2009 addresses several controversial questions on this topic.

After reviewing conflicting evidence AACE/ADA consensus continues to emphasize the importance of glycemic control in hospitalized patients with critical and noncritical illness while aiming at targets that are less stringent than 80–110 mg/dL. AACE/ADA consensus recommends initiating insulin therapy at a threshold of no greater than 180 mg/dL. Once insulin therapy has been started, a glucose range of 140–180 mg/dL is recommended for the majority of critically ill patients. Intravenous insulin infusions are the preferred method for achieving and maintaining glycemic control in critically ill patients. For the majority of noncritically ill patients treated with insulin, the premeal BG target should generally be <140 mg/dL in conjunction with random BG values <180 mg/dL, provided these targets can be safely achieved.

Insulin Regimens in Hospital Setting

To achieve glycemic control, individual physicians often implement a variety of insulin strategies. Some strategies can lead to confusion among the health care staff, others to the use of nonphysiologic sliding-scale insulin protocols that result in poor glycemic control, widely fluctuating blood glucose values, and errors in insulin administration.

The basal-prandial-correction subcutaneous insulin therapy may be appropriate for most hospitalized patients who are eating. It is simple and can be standardized to excellence by the development of institutional order sets or computerized order entry templates. Basal insulin therapy is prescribed as
intermediate-acting insulin neutral protamine hagedorn (NPH) or long-acting insulin analog like insulin detemir. Insulin detemir, in addition to a 24-hr action profile, is associated with less intra- and inter-subject pharmacokinetic variability, which will further reduce the risk of hypoglycemia. Prandial insulin therapy is delivered with meals to prevent excessive glycemic excursions from occurring after ingestion of meals and is prescribed as short human insulin or rapid-acting insulin analog like insulin aspart. Correction-dose insulin therapy is ordered as small doses of short human insulin or rapid-acting insulin analog like insulin aspart delivered to correct hyperglycemia and is prescribed with appropriate timing so as to avoid stacking with previously administered doses of short acting human insulin or rapid-acting insulin analog. Rapid acting analogs like insulin aspart are quickly absorbed; provide better post meal blood glucose control with less risk of hypoglycemia. In addition, the flexibility in meal timing and meal size could be very useful in hospital setting wherein meal time and meal size are uncertain. Subcutaneous insulin therapy with insulin detemir plus insulin aspart is an attractive option for managing hospitalized patients who are eating.

Intravenous insulin infusions are the preferred method for achieving and maintaining glycemic control in critically ill patients. Validated IV insulin infusion protocols with demonstrated safety and efficacy, and with low rates of occurrence of hypoglycemia, are recommended by AACE/ADA consensus. With IV insulin therapy, frequent glucose monitoring is essential to minimize the occurrence of hypoglycemia and to achieve optimal glucose control. Regular human insulin is commonly used for IV infusion. A recent observational study with approximately 3000 subjects has shown that rapid acting insulin analog insulin aspart can be given intravenously for managing inpatient hyperglycemia.

Summary

Current evidence suggests that stringent control of hyperglycemia in critically ill hospitalized patients with diabetes or acute hyperglycemia has been shown to reduce the risk of morbidity and mortality. In view of risk of severe hypoglycemia with near normal blood glucose target, latest consensus is to adopt a less stringent target of 140–180 mg/dl. The development of insulin analogs with more physiologic time-action profiles, improved insulin delivery systems, and standardized protocols for subcutaneous insulin administration and intravenous insulin infusion have improved the safety and convenience of insulin therapy for treating inpatients.

References