Intensive Insulin in the Intensive Care Unit

Introduction

Due to the steady increase in the number of diabetic patients and the fact that as many as 1/3 of hospitalized patients experience stress-induced hyperglycemia, it is important to control hyperglycemia in hospitalized patients. Stress-induced hyperglycemia is commonly seen in critically ill patients in the intensive care unit (ICU), even in those patients who have not been diagnosed with diabetes. Critical illness causes stress on the body and multiple hormones are released in response including epinephrine, glucagon, and cortisol. The release of these hormones results in an increase in the circulating levels of glucose. It has been shown through numerous studies that hyperglycemia and insulin resistance are associated with adverse outcomes. Some of these outcomes include increased mortality, increased risk of wound infections, and impairment of the immune system to fight infection. Administration of insulin to normalize blood glucose levels in critically ill patients has been shown to improve clinical outcomes. Three trials including 2 by Van den Berghe and colleagues and 1 by Krinsley are summarized below.

The first study, a prospective, randomized controlled trial was performed to determine whether normalizing blood glucose levels with intensive insulin reduced morbidity and mortality in critically ill surgical patients. There were 1548 surgical ICU patients randomized to receive intensive insulin or conventional insulin therapy in this study. Patients randomized to receive intensive insulin therapy began treatment when blood glucose was > 110 mg/dL with a goal blood glucose of 80 to 110 mg/dL. Patients in the conventional insulin group began treatment when blood glucose was > 215 mg/dL with a goal blood glucose of 180 to 200 mg/dL. All diabetic and nondiabetic patients admitted to the ICU on mechanical ventilation were eligible to participate. The primary outcome measure was death from any cause while in the ICU. There were multiple secondary outcomes including in-hospital death and length of stay in the ICU. Results revealed that 8% percent of patients in the conventional treatment group died during the ICU stay compared with 4.6% in the intensive insulin treatment group (P<0.04). The intensive insulin group also had fewer patients who died at any point during the hospital stay (7.2% compared with 10.9%; P=0.01). The subset of patients who remained in the ICU for greater than 5 days had the greatest benefit from intensive insulin—20.2% of those patients in the conventional treatment group died compared with 10.6% of patients in the intensive insulin treatment group (P=0.005). Patients who received intensive insulin also had a decreased incidence of septicemia and number of days in the ICU, as well as a reduction in the need for ventilatory support, renal replacement therapy, and transfusions. Hypoglycemia, defined as a blood glucose level ≤ 40 mg/dL, occurred in 39 patients in the intensive insulin group compared to 6 patients in the conventional treatment group. The authors concluded that there was a substantial reduction in mortality and morbidity in critically ill surgical ICU diabetic and nondiabetic patients when blood glucose did not exceed 110 mg/dL.

The second trial was a prospective, randomized controlled study of medical ICU patients whose expected stay in the ICU was at least 3 days. Patients were randomly assigned to either intensive insulin or conventional insulin therapy as in the prior study. The primary outcome was death from any cause in the hospital and the secondary outcomes were similar to the previous study. In this study, 1200 patients underwent randomization; however, there were only 386 patients in the intensive insulin treatment group and 381 patients in the conventional treatment group that remained in the ICU for more than 3 days. Forty percent of patients in the conventional insulin group died compared with 37.3% in the intensive insulin group, which was not a statistically significant difference (P=0.33). However, morbidity was significantly reduced in the intensive insulin group. There was a decrease in newly acquired kidney injury (P=0.04), and an improvement in weaning from ventilator (P=0.05), earlier discharge from the ICU (P=0.04), and overall earlier
discharge from the hospital (P=0.05). Of the patients who were in the ICU for greater than 3 days there was a significant reduction of in-hospital deaths in the intensive insulin group compared to the conventional insulin group (52.5% versus 43%; P=0.009). Hypoglycemia was more common in the intensive insulin group; however, most patients experienced only 1 episode with no complications. The authors concluded that intensive insulin in the ICU prevented morbidity, but did not significantly reduce mortality in all patients and further studies are needed.

A protocol by Krinsley set slightly higher blood glucose goals in patients treated with intensive insulin in a medical ICU. This study examined 800 consecutive patients admitted before initiation of the intensive insulin protocol and compared them to the first 800 patients who were admitted to the medical ICU after initiation of the protocol. Intensive insulin was initiated when 2 consecutive blood glucose readings were greater than 200 mg/dL. The target goal blood glucose in the protocol was less than 140 mg/dL. Mortality was decreased by 29.3% in the protocol period compared to the patients in the historical control group (P=0.002). In addition, there was a decreased length of stay in the ICU, decreased length of stay in the hospital, and a decreased incidence of acquired infections. This protocol for management of hyperglycemia led to improvement of blood glucose levels without an increase in hypoglycemic events. The authors concluded that with use of this intensive glucose management protocol there was a reduction of mortality, organ dysfunction, and length of stay in the ICU.

UIMCC Guideline

UIMCC developed and approved guidelines for administration of intravenous insulin infusion for the adult ICU patient in January 2007. The intention of the UIMCC guidelines is to treat hyperglycemia in both diabetic and nondiabetic patients and prevent complications in this patient population. The guidelines provide the basis for proper monitoring of blood glucose and titration of the insulin infusion to achieve reduced hyperglycemia and avoid hypoglycemia in critically ill patients. The UIMCC guideline and algorithm for initiation and adjustment of the insulin infusion is presented below (updated version 3/07)

**DEFINITIONS**

- **Goal therapeutic glucose concentration:** 80 – 150 mg/dL.
- **Hypoglycemia:** glucose concentration < 60 mg/dL.
- **Symptoms of hypoglycemia:** sweating, tachycardia, palpitations, tremor.
- **Symptoms of severe hypoglycemia:** headache, confusion, visual disturbances, irritability, personality changes, seizures, loss of consciousness.

**POSITION STATEMENTS**

- Sub-optimally treated hyperglycemia is a common problem in the intensive care unit which may lead to an increase in significant complications in this patient population.
- Intensive therapy with insulin, in order to achieve more optimally controlled glucose concentrations, has been shown to potentially decrease ICU length of stay, decrease mortality, improve morbidity and reduce infections, and potentially improve outcomes for patients undergoing cardiac surgery or patients with stroke.
- Insulin infusions are a high alert medication and are dispensed by the pharmacy.
- Patients must be admitted to an adult ICU
- Frequent monitoring of blood glucose (BG) concentrations is critical during infusions.
- This guideline is not intended for the management of hyperkalemia or acute calcium channel antagonist toxicity and does not replace FDA guidelines for insulin infusions in patients with pancreatic transplants.

**PROCEDURE**

1. **General Guidelines:**
   - Standard infusion: 100 Units Regular insulin/100 mL NS via an infusion device.
   - The practitioner may start the insulin infusion when BG is over 150 mg/dL for 2 consecutive readings but individual patients may be started after a single elevated BG based on the degree of glucose elevation and the patient’s history.
   - For most patients, the goal BG should be between 80-150 mg/dL. Physicians may choose a different target BG range if necessary. If a different goal BG is chosen, alterations to the algorithms will be required. Consult with Endocrinology about adjustments.
   - Patients with Type 1 diabetes will require insulin at all times (except while hypoglycemic).
2. Intravenous Fluids:
- A patient who is unable to have enteral feeding, should ideally receive a minimum of 5 grams of glucose per hour in addition to KCl (20 mEq/L) once the glucose is less than 300 mg/dL. This can be provided through intravenous fluid (i.e. D5W at 100 mL/hour or D10W at 50 mL/hour) - the type and rate of which is to be determined by the primary service based on patient factors (i.e. CHF, Renal Failure). Dextrose administration, either orally or through infusions, is important for the prevention of hypoglycemia. Patients with liver or renal disease are especially susceptible because of impaired gluconeogenesis or glycolysis.

3. Initiating the Infusion:
- Algorithm 1: Start here for most patients. (Note exceptions to start in Algorithm 2)
- Algorithm 2: Start here if the patient has a glucose > 600 mg/dL, is in diabetic ketoacidosis, or is s/p CABG, s/p solid organ transplant, receiving glucocorticoids, or patient with diabetes receiving over 80 units/day of insulin as an outpatient, has a BMI more then 35, or is pregnant.
- Algorithms 3-7: Do not start patients in these algorithms.

See Addendum A for Algorithms

4. Adjusting the Rate (See Table 1):

Table 1.

<table>
<thead>
<tr>
<th>Blood Glucose</th>
<th>Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>BG &lt; 60 mg/dL</td>
<td>See Treatment of Hypoglycemia</td>
</tr>
<tr>
<td>BG 61-80 mg/dL</td>
<td>Turn off the infusion and recheck BG every 1 hour until &gt; 80 mg/dL and then restart infusion in next Lower algorithm.</td>
</tr>
<tr>
<td>BG between 80 and 150 mg/dL (goal)</td>
<td>Adjust the rate within the SAME algorithm</td>
</tr>
<tr>
<td>BG between 151 and 180 mg/dL and decreased by 30 mg/dL or more</td>
<td>Adjust the rate within the SAME algorithm</td>
</tr>
<tr>
<td>BG between 151 and 180 mg/dL and did not decrease by at least 30 mg/dL</td>
<td>Adjust the rate to the next HIGHER algorithm</td>
</tr>
<tr>
<td>BG &gt; 180 mg/dL and decreased by 60 mg/dL or more</td>
<td>Adjust the rate within the SAME algorithm</td>
</tr>
<tr>
<td>BG &gt; 180 mg/dL and did not decrease by at least 60 mg/dL</td>
<td>Adjust the rate to the next HIGHER algorithm</td>
</tr>
</tbody>
</table>

5. Treatment of Hypoglycemia: (BG under 60 mg/dL).
- Hold insulin infusion.
- Treat:
  - If patient can take PO, give 15 grams of fast acting carbohydrate (4oz fruit juice/ non diet soda/ 8 oz milk/ 3-4 glucose tablets)
  - If NPO, Give Dextrose 50% inj 25 mL IV Push
- Recheck BG every 15 minutes and repeat above if blood glucose remains less than 60mg/dL.
- Restart infusion once blood glucose is greater than 80 mg/dL. Restart infusion with next lower algorithm. If already on Algorithm 1, reduce Algorithm 1 by half. If pt a known type 2, consider discontinuing insulin infusion.

6. Patient Monitoring:
- Hourly monitoring is indicated for most critically ill patients.
- For stable patients, check BG every hour until it is within goal range (80 – 150 mg/dL) for 4 hours, then decrease BG checks to every 2 hours.

7. Documentation:
- The BG, insulin rate, and algorithm number (i.e. A1 if patient on algorithm 1, A2 if patient on algorithm 2, etc) must be documented on the critical care flow sheet.
- Also document algorithm number under comments in glucose meter
- The BG, insulin rate and algorithm number must also be documented on the transfer sheet when the patient goes to the operating room (OR).
8. Patients Temporarily Leaving the ICU or Requiring Discontinuation of the Insulin Infusion for Reasons Other Than Hypoglycemia
   - Patients should not leave the ICU with a continuous insulin infusion unless the accepting clinician wishes to continue the infusion (i.e. if the patient is going to the OR).
   - The most recent insulin rate, blood glucose and algorithm number must be communicated in writing to the area where the patient is temporarily being transferred.
   - For interruptions anticipated to be only 1 hour or less, discontinue the infusion.
   - For longer interruptions, consider administration of subcutaneous insulin prior to stopping the infusion.
   - To restart the infusion no matter how long the infusion has been off, check the blood glucose and resume the infusion basing the rate on the blood sugar and the PREVIOUS algorithm used prior to stopping the infusion.

9. When Patient is Able to Eat:
   - Once the patient is eating, check a premeal BG and, if necessary, give an additional SQ bolus of rapid-acting insulin after the meal. This is in addition to continuing the IV infusion.

10. Notify the physician:
    - For any blood glucose decrease greater than 150 mg/dL in one hour.
    - For a blood glucose previously under 400 mg/dl and now over 400 mg/dL.
    - For any blood glucose requiring the administration of 25 mL Dextrose 50%.
    - If the patient is unable to tolerate oral or enteral feedings or the dextrose infusion has been discontinued for > 1 hour.

11. Transitioning off the Infusion
    - Insulin infusions should be discontinued when a patient is medically stable and 2hrs after subcutaneous administration of long-acting insulin.

Addendum A:

<table>
<thead>
<tr>
<th>Algorithm 1 BG</th>
<th>Algorithm 2 BG</th>
<th>Algorithm 3 BG</th>
<th>Algorithm 4 BG</th>
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Note: See treatment of hypoglycemia, procedure #5.
P&T Committee Formulary Action
Nov 2006 thru Feb 2007

Additions
- Bumetanide injection
- Sildenafil - Restricted to treatment of pulmonary hypertension

New dosage form, strength or product additions
- Levetiracetam injection - Restricted to Neurology in patients when oral or NG administration is not feasible
- Budesonide respule
- Acetylcysteine (Acetadote) injection - Restricted to treatment of acetaminophen toxicity in patient when oral or NG administration is not feasible
- Pyridostigmine injection – IVP administration restricted to ICU
- Desmopressin tablet
- Papain-urea-chlorophyllin copper complex (Panafil) emulsion topical spray
- Ofloxacin 0.3%, 0.25ml otic singles - OR use only
- Iohexal (Omnipaque) injection
- Milrinone 20mg/100ml D5W RTU
- Triamcinolone acetonide (Kenalog-40) 1ml injection

Deletions
- Quinidine sulfate
- Triamcinolone acetonide (Kenalog-40) 5ml injection

Low use or no longer made
- Theophylline SR capsules
- Varicella Zoster Immunoglobulin
- Diatrizoate meglumine (Hypaque)
- Triamcinolone diacetate (Aristocort)
- Papain-urea-chlorophyllin copper complex (Panafil) topical spray

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