MANAGEMENT OF HYPERGLYCEMIA IN CRITICALLY ILL SURGICAL PATIENTS

SUMMARY

Intensive insulin therapy has been demonstrated to improve outcome in critically ill general surgery patients. Insulin administration should be administered through a standardized protocol in order to improve glycemic control and optimize efficient use of resources. The method of insulin administration should be selected based upon the level of hyperglycemia and consideration of pharmacokinetic principles related to absorption. Given its significant morbidity, consideration of undiagnosed diabetes mellitus is warranted in patients without a prior history and persistent hyperglycemia of uncertain etiology.

RECOMMENDATIONS

- **Level 1**
  - **Intensive insulin therapy in the critically ill patient improves morbidity and mortality, especially among general surgery (non-trauma) patients.**
- **Level 2**
  - **Maintenance of blood glucose (BG) < 140 mg/dL in general surgery patients improves outcome.**
  - **Maintenance of BG < 200 mg/dL in trauma patients improves mortality and reduces infection rate.**
- **Level 3**
  - **Identify iatrogenic causes of hyperglycemia and correct if possible.**
  - **Insulin is the agent of choice for management of hyperglycemia in the critically ill population.**
  - **A standardized protocol should be used to initiate and adjust insulin therapy.**
  - **Continuous intravenous administration of regular insulin is preferred in patients predisposed to erratic absorption who have not achieved adequate glycemic control with subcutaneous administration. If BG > 200 mg/dl on 2 successive measurements, a continuous insulin infusion should be considered.**
  - **Consider addition of basal insulin (NPH) for patients who are receiving enteral nutrition and are persistently hyperglycemic (Table I).**
  - **Consider obtaining a glycosylated hemoglobin (HbA1C) in patients:**
    - **Without a prior history of diabetes mellitus AND**
    - **Persistent hyperglycemia of uncertain etiology AND**
    - **Who have not received massive blood transfusions**

INTRODUCTION

Stress hyperglycemia is a common manifestation of critical illness. Contributing factors include increased secretion of counter-regulatory hormones (i.e., catecholamines, cortisol, growth hormone, glucagon) and

EVIDENCE DEFINITIONS

- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

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insulin resistance due to elevated cytokine levels. Iatrogenic factors include drugs, such as catecholamines and steroids, and infusion of dextrose-containing fluids. Elevated blood glucose concentrations may impair immune function through decreased neutrophil adherence, chemotaxis, phagocytosis, and microbial killing as well as glycosylation of immunoglobulins (1). The clinical consequences of stress hyperglycemia in critically ill patients are variable. Hyperglycemia is associated with an increase in both mortality as well as nosocomial infection in the intensive care unit (ICU) setting (2-5). In the immediate post-operative period, hyperglycemia is an independent predictor of the development of deep sternal wound infections (6,7). In the setting of hypoxic ischemic brain injury, hyperglycemia increases the production of lactic acid resulting in intracellular acidosis (8). This, in turn, propagates the secondary injury cascade. In burn patients, hyperglycemia is associated with enhanced protein catabolism and decreased skin graft take (9,10).

Insulin is the preferred agent for the management of stress hyperglycemia. It has both anabolic and anticatabolic properties and plays a major role in protein, carbohydrate, and fat metabolism. Intensive insulin therapy has been demonstrated to improve morbidity and mortality among the critically ill, but the exact mechanism remains unknown. One theory is that the beneficial effect may be brought about by modulation of asymmetric dimethylarginine concentrations which are higher in critically ill non-survivors and patients with multiple organ failure (11). Insulin dosing in critically ill patients is not well-established. Critically ill patients are predisposed to a number of physiologic alterations that influence insulin absorption and bioavailability when administered by the subcutaneous route. Examples include diminished blood flow secondary to shock and the presence of edema due to resuscitation fluid.

LITERATURE REVIEW

A nomogram for intravenous insulin infusion in critically ill patients was evaluated in a retrospective before-after cohort study (12). Patients in a mixed medical/surgical ICU were compared during two 9-month periods. The sliding scale group was treated using ad hoc sliding scale infusion therapy. The intervention group was treated using a dosing nomogram that was managed by a nurse. The nomogram allowed changes based on both the blood glucose concentration and the concurrent insulin dosage. Infusions in the intervention group were titrated to a target blood glucose concentration of 126-207 mg/dL. The median time until glucose concentrations were < 126 mg/dL was significantly shorter in the nomogram group (2 hours; range 1-22 hours) than in the sliding scale insulin group (4 hours; range 1-38 hours). Glucose control (assessed by determining the AUC of the glucose concentration > 126 mg/dL versus time for the duration of the infusion) was significantly improved in the nomogram group. Episodes of hypoglycemia were similar between groups. Use of the nomogram resulted in a significantly greater number of blood glucose measurements, but with fewer physician orders for changes in the insulin administration regimen.

Development and implementation of a standardized sliding scale insulin protocol resulted in improved blood glucose control and more efficient resource utilization (13). Episodes of glucose measurements < 60 mg/dL or > 400 mg/dL and mean blood glucose concentrations decreased following protocol implementation. In addition, the number of interventions needed to treat hypoglycemia, finger sticks, and calls made to physicians for either high or low readings also decreased.

Normalization of blood glucose levels with intensive insulin therapy in critically ill patients was evaluated to determine the impact on morbidity and mortality (14). Mechanically ventilated patients who were admitted to the intensive care unit were randomized to receive conventional or intensive insulin therapy. In the conventional-treatment group, a continuous infusion of insulin was initiated if the blood glucose level exceeded 215 mg/dL and the infusion was adjusted to maintain a level between 180-200 mg/dL. In the intensive-treatment group, an insulin infusion was initiated if the blood glucose exceeded 110 mg/dL and titrated to maintain a concentration between 80-110 mg/dL. The majority of patients in both the conventional (63%) and intensive (62%) groups were admitted to the ICU following cardiac surgery. Intensive insulin therapy reduced death during intensive care (the primary endpoint) from 8% with conventional treatment to 4.6% ($p<0.04$). The observed reduction in mortality occurred exclusively in patients receiving intensive care for > 5 days where mortality was reduced from 20.2% to 10.6%. Intensive insulin therapy also halved the prevalence of blood stream infection, prolonged inflammation,

acute renal failure requiring dialysis or hemofiltration, critical illness polyneuropathy, and transfusion requirement. Patients receiving intensive insulin therapy were also less likely to require prolonged mechanical ventilation and intensive care. Hypoglycemia (defined as a blood glucose < 40 mg/dL) occurred more frequently in the intensive group (5% versus <1%).

A recent study by the same authors has demonstrated that intensive insulin plays an important role in protecting both the central and peripheral nervous system in critically ill patients with traumatic brain injury (15). Patients receiving intensive insulin therapy demonstrated significantly fewer seizures as well as lower intracranial pressures. Lam et al. similarly demonstrated an association between serum glucose and neurological outcome in a retrospective study of 169 head-injured patients (16). In patients with a GCS < 8, postoperative serum glucose levels >200 mg/dL were associated with a worse outcome (based on GOS) compared to those with a glucose value <200 mg/dL..

Krinsly has confirmed the reduction in ICU mortality, morbidity, and length of stay afforded by maintaining blood glucose levels < 140 mg/dL (17). Gabbanelli et al. have retrospectively demonstrated a reduction in mortality from 26.6% to 13.6% through strict blood glucose control (< 142 mg/dL) (18). Finney and colleagues conducted a prospective observational study to assess the impact of glucose control and insulin administration on ICU patient outcome (19). It showed that increased insulin administration is positively associated with death and glucose control below 144 mg/dl is associated with mortality benefits.

The beneficial effects of hyperglycemic control in the trauma population have been less well established. A retrospective evaluation of the relationship between early hyperglycemia and mortality among 516 non-diabetic trauma patients identified that early hyperglycemia occurred in 483 patients at the ≥110 mg/dL level, 311 patients at the ≥150 mg/dL level, and 90 patients at the ≥200 mg/dL level (20). Only 33 patients had early glucose levels <110 mg/dL. Among patients with glucose levels >150 mg/dL, mortality was 13% and incidence of subsequent infection was 31% versus a mortality of 13% and infection rate of 7% among those <150 mg/dL (p=0.001). Multiple logistic regression (to control for age, Injury Severity Score, admission Glasgow Coma Score, and base deficit) found early blood glucose levels ≥ 200 mg/dL to be an independent predictor of both infection and mortality. Of note, there were some limitations to this study. Hyperglycemia was only assessed during the first 2 days following hospital admission in which the blood glucose values selected were single episodes occurring on day 1 or day 2. Sung et al. also showed in a prospective study that admission hyperglycemia (>200 mg/dl) is associated with poor outcome and increase in infection rate in critically ill trauma patients (21). Yuandemari retrospectively demonstrated that hyperglycemia independently predicts increased ICU and hospital length of stay, incidence of infection, and mortality in the trauma population (22). These associations were noted for both mild hyperglycemia (glucose > 135 mg/dL) and moderate hyperglycemia (glucose > 200 mg/dL).

From an economic standpoint, intensive insulin therapy has been shown to substantially reduce hospital costs (cost saving of 2638 Euros/$3160 per patient) as a result of reductions in ICU length of stay as well as morbidity such as renal failure, sepsis, blood transfusions, and mechanical ventilation dependency (14).

TABLE I: CALCULATION OF NPH DOSE

1. Determine amount of Regular insulin (from infusion or sliding scale) used in the previous 24 hour period.
2. Administer 2/3 of above amount as NPH divided every 12 hours.

TABLE II: TYPICAL INSULIN SLIDING SCALES FOR SURGICAL / TRAUMA PATIENTS

Regular Insulin (subcutaneously)

<60 mg/dL	Initiate hypoglycemia protocol
60-140 mg/dL	0 Units
141-200 mg/dL	5 Units
201-250 mg/dL	10 Units
251-300 mg/dL	15 Units
301-350 mg/dL	20 Units
351-400 mg/dL	25 Units
>400 mg/dL	30 Units

If BG > 150 on two successive measurements, the following intensive sliding scale can be used:

< 60 mg/dl	Initiate hypoglycemia protocol
60-125 mg/dL	0 unit
126- 150 mg/dL	4 units
151-175 mg/dL	8 units
176-200 mg/dL	12 units
201-225 mg/dL	16 units
226-250 mg/dL	20 units
> 250 mg/dL	24 units

If the BG > 200 mg/dl on two successive measurements, a continuous insulin infusion should be considered.

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