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MANAGEMENT OF HYPERGLYCEMIA IN CRITICALLY ILL SURGICAL (NON-CARDIAC) PATIENTS

SUMMARY

Insulin therapy has been demonstrated to improve outcome in critically ill trauma/general surgery patients. Insulin doses should be administered through a standardized protocol in order to improve glycemic control and optimize efficient use of resources. The use of a standard protocol also minimizes the incidence of hypoglycemia which may increase the patients' risk of mortality. 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**
 - Insulin therapy should be used to maintain blood glucose (BG) < 180 mg/dL
- **Level 2**
 - An appropriate therapeutic range for blood glucose control is 110-180 mg/dL in the critically ill non-cardiac surgery patient.
- **Level 3**
 - Insulin therapy should be initiated for a random BG > 150 mg/dL in an effort to keep patients from becoming hyperglycemic (BG > 180)
 - Identify iatrogenic causes of hyperglycemia and correct if possible.
 - Continuous intravenous administration of regular insulin infusions is preferred in patients with erratic absorption, poor perfusion, or those who have not achieved adequate control with subcutaneous insulin therapy
 - A standardized protocol should be used to initiate and adjust insulin therapy
 - Consider the addition of basal insulin (NPH) for patients who are receiving enteral nutrition and are persistently hyperglycemic (Table I)
 - Severe hypoglycemia (BG ≤40) should be treated with intravenous dextrose; mild hypoglycemia (BG 40-70) should be treated based on clinical judgment; for BG 70-110, continue to monitor patient
 - Consider obtaining a glycosylated hemoglobin (Hgb_{A1C}) in patients:
 - Without a prior history of diabetes mellitus AND
 - Persistent hyperglycemia of uncertain etiology AND
 - Who have not received massive blood transfusions

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.

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 insulin resistance due to elevated cytokine levels. Iatrogenic factors include drugs, such as catecholamines and steroids, and the 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. 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 vasopressor administration, large skin/soft tissue wounds/burns, and the presence of edema due to resuscitation fluid.

In an effort to control stress hyperglycemia, both subcutaneous and intravenous insulin have been increasingly utilized in the intensive care unit (ICU). One of the primary concerns regarding the use of insulin is the risk hypoglycemia. The American Diabetic Association (ADA) and the American Association of Clinical Endocrinologists (AACE) defined hypoglycemia in the inpatient setting as a blood glucose (BG) < 70, with severe hypoglycemia defined as a BG < 40 mg/dL (2). Several studies over the last five years have demonstrated that hypoglycemia as a result of intensive insulin therapy (goal blood glucose ~80-100 mg/dL) is independently associated with increased ICU or hospital mortality (2,12-14). Early recognition and treatment of BG levels < 40 mg/dL can prevent progression to more severe episodes with potentially life-threatening sequelae (2).

LITERATURE REVIEW

A nomogram for intravenous insulin infusion in critically ill patients was evaluated in a retrospective before-after cohort study. 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 (15).

Development and implementation of a standardized sliding scale insulin protocol resulted in improved blood glucose control and more efficient resource utilization. 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 (16).

The optimal target blood glucose range for the general surgery, trauma or burn patients remains unclear (2). Recently, several different studies have been conducted comparing intensive (usually 80-110 mg/dL) versus conventional (typically < 200 mg/dL or 180-200 mg/dL) groups (12,17-21). These trials are summarized in Table 1. Four of the trials found no difference in mortality between the two groups (12,18,19,21). Only one trial, predominantly in the post-cardiothoracic surgery population, found a decrease in mortality in the intensive insulin group (17). The largest randomized, controlled trial to date, the NICE-SUGAR Study, found an increase in mortality in the intensive insulin group (19). All of the studies demonstrated a significant increase in hypoglycemia (defined as BG < 40 mg/dL or < 50 mg/dL) in the intensive insulin group as compared to the conventional group (12,17-21). Based on the information provided by these studies, it is clear that maintaining near euglycemia (BG 80-110 mg/dL) is harmful in the critically ill population. Exactly what the upper limit should be, however, remains unclear. Based on the currently available information, the ADA/AACE recommends a target range of 140-180 mg/dL for critically ill patients with some consideration that there may be benefit to targeting the lower end of this range. The ADA/AACE also recommends not lowering the BG below 110 mg/dL (2).

With respect to the cardiothoracic surgery population, Leibowitz G, et.al. conducted a study of consecutive patients undergoing cardiac surgery. The first 8 months of the study, insulin control was based on standard of care; the subsequent eight months, insulin control was based on a standard algorithm with a target of 110-150mg/dL. They enrolled a total of 406 patients. Their results showed overall better glycemic control in the algorithm group along with a decrease in post-operative infections, atrial fibrillation, multiorgan failure, and need for prolonged mechanical ventilation ($p < 0.05$). There was no difference in mortality between the two groups (22).

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 (15).

TABLE 1. Summary of Glucose Control Studies

Study	Population	n	Goal Glucose Intensive vs Control		Outcomes	Hypoglycemia Intensive vs Control	
Van den Berghe (17)	63% cardiothoracic surg 15% other surg 12% other	Intensive n=765 Control n=783	80-110	180-200	<ul style="list-style-type: none"> • 32% reduction mortality (p<0.04) 	5%	0.8%
Van den Berghe (18)	MICU patients	Intensive n=595 Control n=605	80-110	180-200	<ul style="list-style-type: none"> • No difference in mortality • More hypoglycemia in intensive group 	*18.7%	3.1%
Arabi (19)	16% Post-op 85% ventilated 21-26% sepsis 15-21% TBI	Intensive n=266 Control n=257	80-110	180-200	<ul style="list-style-type: none"> • No difference in mortality • More hypoglycemia in intensive group 	*28.5%	3.1%
NICE SUGAR (20)	37% Post-op 14-15% Trauma 21-22% severe sepsis	Intensive n=3016 Control n=3014	81-108	< 180	<ul style="list-style-type: none"> • Higher mortality in intensive insulin group (p=0.04) • More hypoglycemia in intensive group 	*6.8%	0.5%
Bilotta F (21)	Neurosurgery 20-21% TBI	Intensive n=241 Control n=242	80-110	180-215	<ul style="list-style-type: none"> • More hypoglycemia in intensive group (p=0.0001) • Shorter ICU LOS in intensive group • Fewer ventilator days in intensive group • No difference in mortality • No difference in GOS 	†94%	63%
Preiser JC (12)	40-42% Medical 30-32% Elective surgery 17-18% Emergency surg 8% Trauma	Intensive n=536 Control n=542	79-110	140-180	<ul style="list-style-type: none"> • No difference in mortality • More hypoglycemia in intensive group • Hypoglycemia a risk factor for mortality 	*8.7%	2.7%
Leibowiz G (22)	Cardiothoracic surgery	Algorithm n=203 Control n = 203	110-150	Undefined	<ul style="list-style-type: none"> • No difference in mortality • Decreased infections 	3%	2.5%

MICU = medical intensive care unit; surg = surgery; Post-op = post-operative; TBI = traumatic brain injury

*p<0.05 compared to control group for higher rate of hypoglycemia (blood glucose < 40 mg/dL)

†p<0.0001 compared to control group for higher rate of hypoglycemia (blood glucose < 50 mg/dL)

TABLE 2: CALCULATION OF INITIAL 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 3: TYPICAL INSULIN SLIDING SCALES FOR SURGICAL / TRAUMA ICU PATIENTS

Insulin: Regular Insulin (subcutaneously)

Standard Sliding Scale (recommended frequency Q4H or Q6H)

< 70 mg/dL	Initiate hypoglycemia protocol
70-140 mg/dL	0 units
141-200 mg/dL	5 units
201-250 mg/dL	10 units
>250 mg/dL	15 units

Intensive Sliding Scale (recommended frequency Q4H)

Consider initiating if BG > 150 mg/dL on two successive measurements

< 70 mg/dL	Initiate hypoglycemia protocol
70-125 mg/dL	0 units
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 BG > 200 mg/dL on two successive measurements, a continuous insulin infusion should be considered.

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