Review Article

Management of Hyperglycemia in Critically ill patients

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Abstract:

Hyperglycemia defined as random blood glucose > 200 mg/dl is extremely common in critically ill patientsIt could be a manifestation of uncontrolled Diabetes exacerbated by critical illness or could be undiagnosed diabetes which becomes overt due to critical illness. Whatever the mechanisms; hyperglycemia is an independent predictor of outcome in critically ill patients However there are a lot of controversies regarding the target Glucose levels and protocols of Insulin administration . We would like to discuss these issues in brief and put forth the most accepted guidelines for management of hyperglycemia in critically ill patients.

Introduction

Hyperglycemia defined as random blood glucose > 200 mg/dl is extremely common in critically ill patients. It could be a part of Stress mechanism; referred to as ' Stress Induced Hyperglycemia (SIH)'[1]. It could be a manifestation of uncontrolled Diabetes exacerbated by critical illness or could be undiagnosed diabetes which becomes overt due to critical illness. Whatever the mechanisms; hyperglycemia is an independent predictor of outcome in critically ill patients. However there are a lot of controversies regarding the target Glucose levels and protocols of Insulin administration [2,3]. We would like to discuss these issues in brief and put forth the most accepted guidelines for management of hyperglycemia in critically ill patients. Also we have not included management in specific situations like Acute myocardial infarction, Stroke etc. as it is beyond the scope of this review.

Prevalence

Stress-induced hyperglycemia, has been described in 5 to 30% of critically ill patients. Approx. 5% patients are newly diagnosed diabetics. The prevalence of diabetes in hospitalized adult patients is not known, however, more than 50% of hospitalized patients with hyperglycemia do not have a diagnosis of diabetes [1]. Approximately 75% of all patients, including diabetics, have blood glucose concentrations > 110 mg/dL at the time of admission, and 12% of all patients have blood glucose concentrations > 200 mg/dL[4]. . Although Indian data reveal that every sixth patient admitted to hospital has diabetes, in reality the number may be higher[5].

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Hyperglycemia has been linked to worse outcomes in critically ill patients. In 2001,the Leuven study demonstrated that tight glycemic control with a target of blood glucose level between 80 and 110 mg/dL had better outcome than conventional control in critically ill surgical patients. ICU mortality, the risk of multi-organ failure, systemic infection and sepsis, the incidence of acute renal failure, critical illness-related polyneuropathy, the need for blood transfusion, and the need for prolonged mechanical ventilator support were reduced [4]. The SPRINT study showed that tight glycemic control to a mean of 6.0 mmol/L mitigated organ failure faster than conventional control at a higher mean level of 7.2 mmol/L[6]. Patients with SIH had worse outcomes than patients with a known diabetic history. Umpierrez et al reported that newly diagnosed hyperglycemia (admission or fasting glucose level > 125 mg/dL or random glucose level > 200 mg/dL) was associated with a 16% mortality rate compared to a mortality rate of 3% among patients with known diabetes and a rate of 1.7% among patients without hyperglycemia. Three cohorts of ICU patients concluded that hyperglycemia during an ICU admission had a more significant impact on the risk of mortality among patients without diabetes than among patients with diabetes [7].

Mechanism of Hyperglycemia in critically ill

Stress-induced hyperglycemia, described in 5 to 30% of critically ill patients, is believed to be secondary to increased levels of stress hormones. During acute illness, stress hormones are produced which increase insulin resistance by increasing hepatic glucose production and decreasing peripheral glucose uptake[8]. Over the short term, hyperglycemia can adversely affect fluid balance and immune function, and it can promote inflammation.4 Hyperglycemia negatively affects many body systems, including the cardiovascular (acute myocardial ischemia,

cardiogenic shock, arrhythmias), neuromuscular (polyneuropathy), immunologic (immunosuppression, nosocomial infections) and cerebral (ischemic stroke), and also impairs wound healing. In critically ill patients, besides maintaining euglycemia, insulin has beneficial multi-factorial actions in each of these body systems, as well as in wound healing [9].

Use of medications (exogenous glucocorticoids, vasopressors, lithium, and β-blockers). Over feeding, intravenous dextrose, commonly used parenteral nutrition, dialysis solutions, and antibiotic solutions, also contribute to hyperglycemia. Insufficient insulin or volume depletion can cause hyperglycemia. Bed rest, even in the absence of obvious disease, leads to impaired skeletal muscle glucose uptake and promotes peripheral insulin resistance. In patients with diabetes, the cause of hyperglycemia is a combination of insulin resistance and pancreatic β-cell secretory defects [10]. TNF-α may promote gluconeogenesis by stimulating glucagon production. Glycogenolysis is triggered primarily by catecholamines and perpetuated under the influence of epinephrine and cortisol. The action of counter-regulatory hormones on insulin resistance in skeletal muscles may be mediated through an elevation in the circulating free fatty acid level in patients with critical illness, despite hyperinsulinemia. Cytokines such as TNF-α and IL-1, inhibit post-receptor insulin signaling[11].

Guidelines for Glycaemic control

There have been many studies which have used different targets for Glycaemic control in critically ill patients. Mortality due to hypoglycaemia has been a cause for concern in most of the trials. Such trials have not been carried out in India and hence we have to use the guidelines recommended by west.

AACE / ADA guidelines were published in 2009. Initially they recommended lower targets but In May 2009, AACE/ADA revised their inpatient glycemic targets to 140–180 mg/dL in the ICU and non-ICU preprandial glucose levels below 140 mg/dL and all random glucose levels below 180 mg/dL. In addition they gave following recommendations for management of hyperglycaemia in critically ill patients [12].

1) identify elevated BG in all hospitalized patients;
2) establish a multidisciplinary team approach to diabetes management in all hospitals;
3) implement structured protocols for aggressive control of BG in both ICUs and other hospital settings;
4) create educational programs for all hospital personnel caring for people with diabetes; and
5) plan for a smooth transition to outpatient care with appropriate diabetes management.

These guidelines give institutions structure to develop protocols that achieve BG goals yet allow for individualization of algorithms and policies to fit with the hospital's culture and environment.

In 2011, The American College of Physicians further relaxed the target blood glucose levels upto 200 mg/dl [13]. The authors recommend the use of current glycaemic goal in critically ill patients as 140 -180 mg /dl.

Management of Hyperglycaemia in critically ill patients

Specific clinical recommendations for critically ill patients are as follows[12]:

For treatment of persistent hyperglycemia, beginning at a threshold of no greater than 180 mg/dL (10.0 mmol/L), insulin therapy should be started.

For most critically ill patients, a glucose range of 140 to 180 mg/dL (7.8 - 10.0 mmol/L) is recommended once insulin therapy has been started.

To achieve and maintain glycemic control in critically ill patients, the preferred method is intravenous insulin infusions.

Validated insulin infusion protocols that are shown to be safe and effective and to have low rates of hypoglycemia are recommended.

To reduce hypoglycemia and to achieve optimal glucose control, frequent glucose monitoring is essential in patients receiving intravenous insulin.

Tight glycaemic control Vs. Optimal glycaemic control

This has always been a matter of great discussion and many trials were done to validate the glycaemic approach. Two significant studies, the Leuven study by Van den Berghe [4] and the Diabetes Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) Trial [14], had overturned traditional approaches in critical care diabetes management. These studies have confirmed that intensive glucose management of hyperglycemia, via continuous insulin infusions, reduces mortality in a largely non-diabetic, critically ill population. Furthermore, management of hyperglycemia through the use of insulin infusion protocols ushered a new standard in critical care. Later on many studies focused on Intensive Glucose control in critically ill and targets were brought down from 180 mg/dl to as low as 110 mg/dl.

However Subsequent studies were unable to reproduce the promising results of Leuven 1. A higher incidence of severe hypoglycemia was observed with intensive glycemic therapy in other studies, one of which was

terminated early due to safety concerns. One study included patients with severe sepsis, who may be at higher risk for hypoglycemia at presentation [15,16]. The recently published Glucontrol study compared intensive insulin therapy (BG target 80–100 mg/dl) with an intermediate BG target (140–180 mg/dl) in 1101 patients in a mixed MICU/SICU. This study was stopped prematurely due to poor compliance with study protocol. There was more hypoglycemia and no mortality benefit with intensive insulin therapy [17].

The NICE-SUGAR study (Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation) is the largest RCT of intensive vs. conventional insulin therapy.In March 2009, it reported higher mortality and hypoglycemia rates in ICU patients treated with intensive glycemic control (80110 mg/dL) compared to less tight glycemic control (glucose <180 mg/dL).[34] The conventional group in NICE-SUGAR, however, required insulin 69% of the time in order to achieve the target glucose below 180 mg/dL, indicating a continued need for insulin therapy in the majority of critically ill patients just with a less intensive glucose target range [18].

In short the Meta-analysis of many clinical trials have not shown mortality benefit with tight glycaemic control, hence ACP has given following recommendations [13].

Recommendation 1: ACP recommends not using intensive insulin therapy to strictly control blood glucose in non-SICU/MICU patients with or without diabetes mellitus (Grade: strong recommendation, moderate-quality evidence).

Recommendation 2: ACP recommends not using intensive insulin therapy to normalize blood glucose in SICU/MICU patients with or without diabetes mellitus (Grade: strong recommendation, high-quality evidence).

Recommendation 3: ACP recommends a target blood glucose level of 7.8 to 11.1 mmol/L (140 to 200 mg/dL) if insulin therapy is used in SICU/MICU patients (Grade: weak recommendation, moderate-quality evidence).

Insulin infusion Protocol for management of Hyperglycemia in critically ill patients

- All major studies have recommended the use of Insulin Infusion for management of hyperglycemia in critically ill patients. Once a critically ill patient is admitted to ICU, ADA recommends that [19,20]
- For all patients with diabetes, clearly document diabetes in medical record
- Order blood glucose monitoring for all patients with results made available to healthcare team
- Goals for blood glucose levels in critically ill patients
- Initiate insulin for treatment of persistent hyperglycemia starting at threshold of ≤180 mg/dL (10.0 mmol/L); once insulin is started, 140–180 mg/dL (7.8–10.0 mmol/L) is recommended range for most patients
- More stringent goals may be appropriate for certain patients, especially in SICU
- IV insulin protocol with demonstrated efficacy, safety in achieving glucose targets with no increased hypoglycemia risk .

Patient type	Glycaemic goals	Preferred Insulin type
Critically ill patients	140–180 mg/dL	IV insulin infusion
		• Initiate insulin at glucose >180g/dmL • Maintain glucose 140–180 mg/dL • Glucose <110 or >180 mg/dL not recommended
Non-critically ill patients		
• Preprandial blood glucose	<140 mg/dL	Subcutaneous insulin
• Maximum blood glucose	<180 mg/dL	• Basal insulin • Nutritional or mealtime insulin • Correctional dose insulin

Insulin administration

A. ***Sliding scale Insulin :*** Unless the hyperglycemia is mild and expected to be transient, regular insulin sliding scales should not be used alone in hospitalized patients. Regular insulin, when given subcutaneously every 6 h without basal insulin, creates periods of insulin deficiency. Furthermore, if the blood glucose is normal, most sliding scales do not call for insulin, and thus no basal insulin is provided and hyperglycemia recurs.

B. A continuous intravenous insulin infusion in the critically ill patient with type 2 diabetes provides optimal glycemic management. Alternatively, basal insulin for patients with type 2 diabetes may be provided with NPH, lente, or ultralente insulin at a starting dose of 0.4–0.6 U/kg/d in equally divided doses every 8–12 h. If the patient is relatively thin or has comorbidities that increase the risk for hypoglycemia (hepatic dysfunction or renal failure), a more conservative basal dose of 0.2 U/kg/d may be utilized. In addition to basal insulin coverage, additional short acting insulin to manage acute hyperglycemia (given subcutaneously as regular or lispro insulin every 4–6 h) should be used. For patients who are eating, we suggest a meal dose 0.05 U/kg/meal for insulin-sensitive patients or 0.1 U/kg/meal for insulin-resistant patients [21].

C. Continuous subcutaneous insulin infusion in Type I diabetics and Type II diabetics having insulin pump –

Some recommend that in critically ill patients CSII should be discontinued and these patients should be temporarily switched over to IV insulin infusion because it requires a trained staff to monitor and adjust the doses. Moreover the personnel should be familiar with the use of the system. In case the patient is alert and is able to understand the protocol and adjust insulin dose accordingly CSII may be continued [22].

Insulin infusion protocols

There are numerous protocols which have been described for administration of Insulin to critically ill patients. The modified Yale Insulin protocol is practiced a lot. However there are no Indian guidelines formulated on the basis of Indian data. Following protocol given by Bajwa S S et al. can be used. It is recommended that each hospital should have its protocol based on the patient characteristics, Insulins used, monitoring methodology and available resources [23].

Suggested protocol for Insulin infusion in ICU

A. Preparation: 50 units of regular insulin dissolved in 50 mL normal saline (NS) in a 50 mL disposable syringe

B. Mode of administration: IV infusion with an electronic syringe pump/infusion pumps

C. Primary target: To maintain blood sugar level within a predefined target 140 mg/dL

D. Control methodology: Blood sugar to be controlled gradually in case of severe hyperglycemia by titrating the dose of IV insulin

E. Pre-requisites: Initially 15–20 mL of solution should be flushed through plastic tubing to saturate the insulin binding sites in the tubing

F. Targets Dose: should be adjusted as per the levels of blood sugar

G. Monitoring: Either by capillary blood glucose or from the venous site/central line.

Titration of insulin dose according to blood glucose (BG) levels

Blood glucose levels (mg/dL)	Dosage of insulin infusion
< 100	No insulin to be given
100–149	1–1.5 units/hour
150–199	2 units/hour
200–249	2.5 units/hour
250–299	3 units/hour
300–349	3.5 units/hour
350–399	4 units/hour

- For any further increase in BG, consulting endocrinologist/physician/intensivist needs to decide the rate subjectively.
- If BG does not fall more than 10%, insulin can be increased to 1.5 times the normal dose.
- If BG is < 50 mg/dL Administer 50 mL of dextrose (25 g), check blood sugar at 15 minutes and if blood glucose increases to more than 100 mg/dL, start insulininfusion after 1 hour
- BG between 50 mg/dL and 75 mg/dL Infuse 50 mL dextrose (25 g) if hypoglycemia manifests clinically. If asymptomatic, give half dose of the above solution. Check blood sugar after 15 minutes and start insulin 1 hour after BG reaches > 100 mg/dL.

Blood Glucose monitoring

It can be performed by capillary glucose monitoring, venous blood sampling or arterial blood sampling if patient has an arterial line.

- Initially 1 hourly monitoring should be done till target glucose values are achieved.
- When 3 consecutive values are within the target range, 2 hourly monitoring should be done.
- Once the target glucose values are maintained for 24 hours, 4 hourly monitoring can be done.
- If there is recurrence of hyperglycemia, frequency of monitoring should be increased.
- Once patient starts taking orally, glucose monitoring should be structured to patients meal times and appropriate treatment should be given.

Transition to subcutaneous Insulin therapy after initial Insulin infusion

- Calculate 24 hours insulin requirement
- 50% should be given as basal insulin
- 50% should be given as bolus insulin in divided doses before each meal
- Monitor fasting, pre and 1 hour post meal glucose values
- Additional correction bolus insulin should be given for all readings above 140 mg/dl

$$\text{Correction Bolus formula} = \frac{\text{Current Glucose} - \text{desired glucose}}{1700 \,/\, \text{Daily requirement of Insulin}}$$

Newer Protocols

1. ***Computerized Dosing algorithm:*** Using a computerized insulin dosing algorithm to manage hyperglycemia with particular attention to frequency and conditions surrounding hypoglycemic events. 4,588 ICU patients were treated with the Gluco

Stabilizer to a BG target range of 4.4-6.1 mmol/L. The mean BG (+/- SD) after achieving target was 5.4 (+/- 0.52) mmol/L. Targeted blood glucose levels were achieved at similar rates with low incidence of severe hypoglycemia in patients with and without diabetes, sepsis, renal, and cardiovascular disease [24].

2. ***Enhanced model predictive control (eMPC) algorithm***

   The eMPC includes a model of the glucoregulatory system, which adapts itself to the input-output relationship observed during tight glucose control; that is, an incoming glucose measurement is used by the model to update model parameters such as insulin sensitivity taking into account previously given insulin and parenteral and enteral glucose. Once individualized to a critically ill subject, the eMPC uses the glucoregulatory model to determine the optimum insulin infusion rate which is expected to achieve the target glucose concentration. It performed better to achieve Target Glucose concentration, minimizing the risk of hypoglycemia as compared to other protocols [25].

3. The SPRINT (Specialized Relative Insulin and Nutrition Tables) protocol: It is the only protocol that reduced both mortality and hypoglycemia by modulating both insulin and nutrition, but it has not been tested in independent hospitals. The glycemic performance shows that using the SPRINT protocol to guide insulin infusions and nutrition administration provided very good glycemic control in initial pilot testing, with no severe hypoglycemia [26].

Use of newer insulins : Usually rapid acting Insulin is used but newer Insulins like Insulin Aspart or Insulin Lispro can also be used. Insulin Glargine can be used as basal insulin in transition period. Trials of newer insulins in critically ill patients are yet to come.

Hypoglycemia

Hypoglycemia is the limiting factor to aggressively normalizing blood sugars in all patients. Hypoglycemia is an independent predictor of hospital mortality. In the largest review of hospital glucose data of more than 12 million blood sugars at 126 U.S. hospitals, 10.1% of all blood sugars in the ICU setting were in the hypoglycemic range (defined as a glucose <70 mg/dL) and 3.5% of all blood sugars in non-ICU patients indicated hypoglycemia. In a study of more than 100,000 inpatient admissions in patients with diabetes, patients who experienced hypoglycemic episodes had longer hospital stays, a 7% higher risk of inpatient mortality, a 39% increase in hospital costs, and a 58% increase likelihood of discharge to a skilled nursing facility. Preventing and minimizing the incidence and severity of hypoglycemia is possible with the use of standardized insulin protocols, hypoglycemia protocols, and the use of insulin analogs [27,28].

Glycaemic variability

Blood glucose levels in critically ill patients fluctuate widely, even when continuous feeding and an insulin infusion are used. Glycemic variability is usually expressed as the standard deviation around the mean glucose value or as the mean amplitude of glycemic excursions. Glycemic variability is also associated with outcome in critically ill patients; specifically, greater glycemic variability is associated with a significantly higher mortality rate. A blood glucose level standard deviation > 20 mg/dL was associated with a 9.6-fold increase in mortality compared with a blood glucose level standard deviation < 20 mg/dL [29,30]. Hence the therapeutic regimens should target Glycaemic variability to reduce mortality in critically ill patients.

Conclusion

Hyperglycemia is associated with increased mortality in critically ill patients, more in nondiabetic than diabetic patients.

Currently recommended Blood glucose target of 140-180 mg/dl should be maintained with appropriate insulin infusion protocol, with frequent monitoring of blood glucose values and preventing hypoglycemia. Glycaemic variability should also be addressed while managing hyperglycemia in critically ill patients.

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