Review Article

Management of Hyperglycemia in Critical Illness : Review of Targets and Strategies

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Introduction

Diabetes mellitus is a common problem and stress related hyperglycemia occurring in patients without history of diabetes mellitus has been shown to be associated with a poorer clinical outcome [1-3]. Effective glycemic control in critically ill patients results in marked improvements in clinical outcome [4,5]. Approximately 12% of all hyperglycemic patients being admitted to tertiary care setting have no previous diagnosis of diabetes [6]. Sixty percent of patients with admission hyperglycemia developed confirmed diabetes at one year in a small study [7].

Pathophysiology of Stress Induced Hyperglycemia

Stress hyperglycemia is usually defined as newly detected hyperglycemia (>200 mg/ dl) which resolves after resolution of acute illness. Two diagnostic categories of stress hyperglycaemia have been proposed:

a) Hospital- related hyperglycemia according to the American Diabetes Association (ADA) consensus definition (fasting glucose >126 mg/ dl or random glucose >200 mg/dl without evidence of previous diabetes), and

b) Pre-existing diabetes with deterioration of pre-illness glycemic control [8].

Hospital related hyperglycemia is a common problem which results from activation of insulin counter regulatory hormones caused by stress. Glycemic control is further impaired by administration of drugs which increase insulin resistance such as catecholamines and steroids. Severe hyperglycemia is a catabolic state associated with adverse electrolyte and volume shifts [9]. Mechanisms include high tissue and circulatory concentration of inflammatory cytokines and a reduction of glucose uptake capacity in peripheral tissues [10,11]. There is increased hepatic glucose production, depressed glycogenesis, and glucose intolerance.

Increased production of counter regulatory hormones i.e. glucagon, catecholamines, cortisol and growth hormone increases insulin resistance thereby decreasing insulin action [1]. Tumour necrosis factor α (TNF-α) has also been shown to have a role in the insulin resistance most likely through the modification of signaling properties of insulin receptor substrates. Insulin resistance ultimately promotes a catabolic state leading to lipolysis and lipotoxicity which further aggravates the inflammatory state [12].

These cumulative metabolic alterations result in hyperglycemia, glucosuria, ketonuria, osmotic diuresis and loss of water and electrolytes resulting in dehydration, hemodynamic instability and poor tissue perfusion. Osmotic diuresis can predispose to symptomatic hyponatremia. Loss of lean body mass, negative nitrogen balance causes impaired healing and decreased resistance to infection.

Impact of Hyperglycemia: Current Evidence

Patients with stress hyperglycemia and no previous diagnosis of diabetes face worse consequences at a given severity of hyperglycemia than do those with pre-existing diabetes [8]. Whether stress induced hyperglycemia per se causes harm or is a marker of severity of counter regulatory hormone release, inflammatory response and degree of illness is not known [12]. Chronic hyperglycemia may induce protective cellular conditioning for example, down regulation of glucose transporters which would protect cells from unchecked glucose ingress. Such a response would be lacking in those developing stress related hyperglycemia.

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Intensive care unit (ICU) Admissions: Among patients admitted to ICU, those with newly diagnosed hyperglycemia had 3-fold higher mortality rate (31%) than patients with known history of diabetes (10%) or, with normo-glycemia (11.3%) [1]. A retrospective analysis of a heterogeneous group of critically ill patients in ICU revealed that mean and maximum glucose values were significantly higher among non survivors than among survivors for the entire group [2]. The lowest mortality (9.6%), occurred among patients with mean glucose values between 80 and 99 mg/dL and increased progressively as glucose values increased, reaching 42.5% among patients with mean glucose values exceeding 300 mg/dL. Within each of 3 groupings of Acute Physiology and Chronic Health Evaluation II (APACHE II) scores (0-14; 15-24; ≥ 25), mean and maximum glucose values were higher among non survivors than among survivors [2].

In general surgery patients, the relative risk for serious post-operative infections (sepsis, pneumonia, and wound infection) increased 5.7 fold when any post-operative day 1 blood glucose (BG) was ≥ 220 mg/dl [13]. The prospective study by Berghe et al [5] in mechanically ventilated adults in surgical ICU showed that keeping the blood glucose level between 80-110 mg/dl by continuous intravenous insulin infusion reduced overall in-hospital mortality by 34%, bloodstream infections by 46%, acute renal failure requiring dialysis or haemo filtration by 41%, the median number of red cell transfusions by 50% and critical illness polyneuropathy by 44%. The greatest reduction in mortality was from deaths caused by multiple organ failure with a proven septic focus. These results were not replicated in a subsequent study by the same group in medical ICU patients and hypoglycemia emerged as an independent predictor of death [4].

Acute myocardial infarction: In diabetes mellitus, insulin glucose infusion in acute myocardial infarction (DIGAM I), intensive treatment by use of insulin infusion in acute MI resulted in 29% lower mortality compared to the conventionally treated group [14]. DIGAMI 2 however, failed to show similar results [15]. Plasma glucose at admission also appears to be an independent predictor of long-term outcome in non-diabetic patients with acute myocardial infarction (AMI) [3]. During 1.5-2.5 year follow up of patients with AMI < 30% died, 10% were re hospitalized for heart failure, and 6% for nonfatal reinfarction. All of these patients had significantly higher blood glucose compared to patients who did not have these complications [3]. In an analysis of 15 studies, patients without diabetes who had glucose level more than or equal to range of 110-145 had a 3.9 fold higher risk of death than patients without diabetes who had lower blood glucose levels. In patients with acute MI, admission blood glucose levels more than 180 mg/dl were associated with increased risk of congestive cardiac failure or cardiogenic shock [16].

Acute Stroke: Hyperglycemia in the acute phase of stroke has been established as a predictor of poor outcome in non-diabetic patients [17,18]. Bruno et al [18] reported worse neurological outcome at three months in ischemic stroke patients admitted with higher blood glucose level according to multivariate logistic regression analysis adjusted for stroke severity, diabetes mellitus and other vascular risk factors. Hyperglycemia was also found to be the only independent predictor of haemorrhagic transformation of ischemic stroke in one study [19]. The mechanism by which hyperglycemia might influence stroke outcome is uncertain. Both acute and chronic hyperglycemia is associated with increased edema and infarct size and with reduced cerebral blood flow and cerebrovascular reserve. There is also accumulation of extracellular glutamate, blood brain barrier disruption and tendency for haemorrhagic transformation. Hyperglycemia exacerbates local production of lactic acid, hence intracellular pH is lowered and cells die or become dysfunctional [17].

In-Hospital patients: A recent study revealed that hyperglycemia was not only an independent marker of in-hospital mortality in ICU but also in patients admitted to general hospital wards [1]. In this study, investigators divided patients into three groups: those with a known history of diabetes, those with new hyperglycemia and those with normoglycemia. Total mortality was significantly higher in patients with new hyperglycemia (16%) than in diabetic patients (3%) and normoglycemic patients (1.7%). The difference in mortality between the first and third groups is striking: nearly 10 times as many deaths among new hyperglycemic patients than among normoglycemic ones. Patients with new hyperglycemia had a longer mean hospital stay (nine days) compared to patients with known diabetes (5.5 days) and those with normoglycemia (4.5 days). Another interesting finding was that new hyperglycemia was frequently left untreated. Only 13% of patients had orders for a diabetic diet; 2% were prescribed oral hypoglycemic agents; 6% received scheduled insulin regimens; and 35% received sliding-scale insulin [17].

Numerous studies have reported that besides saving lives, intensive insulin therapy can prevent complications such as severe nosocomial infections, acute renal failure, hepatic dysfunction, critical illness polyneuropathy, muscle weakness and anaemia, thus improving overall outcome [6].

Treatment Targets

Traditionally, hyperglycemia is managed with the aim of keeping blood glucose levels high enough to avoid hypoglycemia, but low enough to avoid excess catabolism, ketoacidosis, hyperosmolality and risk of infection. Targets ranging from 120-250 mg/dl [2-20] have been advocated.

The push towards tighter glycemic control was provided by the landmark study by Berghe et al [5], which showed that in critically ill patients admitted to surgical ICU, intensive insulin therapy resulted in reduction of mortality from 8 to 4.6%. These impressive results failed to be replicated in a subsequent study by the same author in patients admitted to medical ICU. On the contrary, an in hospital mortality of 75% for those developing insulin related hypoglycemia was reported [4].

A recent meta analysis by Griesdale et al [21] concluded that intensive insulin therapy had no effect on mortality in critically ill patients. Such therapy may possibly benefit patients in surgical ICU, but a six fold increase in incidence of serious hypoglycemia was also noted. The recently reported Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation (NICE-SUGAR), a large multi center randomised controlled trial comparing conventional (<180mg/dl) to tight (80-110mg/dl) glycemic control using iv insulin infusion in ICU patients showed increased mortality for patients in the intensive group [23]. The mean blood glucose in conventional group was 144 ± 23 mg/dl vs. 115 ± 18mg/dl in the intensive control group. Severe hypoglycemia (<40mg/dl) was recorded in 6.8% in intensive control group vs. 0.5% in conventional group.

Insulin Therapy

Despite calls for its abolition, inpatient hyperglycemia care still frequently relies on sliding scale of insulin (SSI) protocols. The use of SSI was first introduced by Elliot P. Joslin shortly after the discovery of insulin regular insulin was prescribed per sliding scale according to the amount of glucosuria [23]. Potential advantages of SSI are convenience, simplicity, and promptness of treatment. However, a major shortcoming is that it treats hyperglycemia after its occurrence rather than preventing it leading to wide glycemic fluctuations. Review of literature reveals that blood glucose control with such regimes is almost always poor and has unproven efficacy. Umpierrez et al [23] conclusively demonstrated superior glycemic control without increasing risk of hypoglycemia in an inpatient cohort given scheduled basal bolus insulin compared with sliding scale.

In septic patients, glucose variability has been shown to be independently associated with hospital mortality [24]. Glucose fluctuations may trigger adverse events beyond those resulting from hyperglycemia viz increased apoptosis, cytokine expression and oxidative stress [25]. Thus, control of variability appears to be a key feature of optimizing outcome in hyperglycemic patients.

Continuous intravenous insulin infusion is the most rational and physiologic method of management of hyperglycemia in ICU. Various studies have demonstrated that this method is safe, effective and flexible [2,26-28]. It is imperative however to monitor blood glucose hourly and titrate the rate. This would necessitate adequate staffing of the ICU.

Regimen for Continuous Insulin Infusion

There is no absolute method to determine exact requirement of insulin in a given patient. Therapy needs to be individualized and customized to the need of the patient. Insulin can be started either as insulin and glucose infused separately or glucose insulin potassium (GIK) combined solution. While a number of validated and effective protocols for insulin infusion are in use [6,20,27,29], we suggest the following as a simplified method.

Protocol for GIK Solution (*Adapted from The Glucose Insulin in Stroke Trial)* [27]: This is acceptable for patients with hyperglycemia not permitted oral feeding. Prepare GIK solution in 500 ml 5% dextrose solution with 10 meq of potassium and add 10 units of short acting insulin and start infusing at a uniform rate (usually 100 ml/ hr). Prepare two more GIK solutions, one with 15 and the other with 5 units of insulin. If blood glucose falls below 100 mg/ dl then change to drip with 5 units of insulin and if blood glucose is more than 200 mg/ dl replace initial drip with the one with 15 units insulin. Once target levels are attained continue with the concentration and rate to maintain levels if blood glucose level rises unexpectedly, it is better to switch over to separate drip method. Alternatively, a supplemental subcutaneous bolus of regular insulin may be administered if patient is haemodynamically stable.

1. Add 15 unit of regular insulin in 500 ml 5% dextrose with 10 meq KCl
2. Start at the rate of 100 ml/hour
3. Adjust the dose according to blood glucose levels

   100-200 mg/ dl : continue the drip

   <100 mg/ dl : decrease insulin concentration by 5 units

   >200 mg/ dl : increase insulin concentration by 5 units

   >300 mg/ dl : give supplemental dose of 5 units regular insulin subcutaneously if patient is

haemodynamically stable, or, switch over to separate drip method.

Protocol for separate insulin glucose infusion (*Modified from Yale IIP)* [29]: Prepare insulin drip by adding 50 units of human regular insulin to 500 ml of normal saline. Infusion set should be flushed with 30 ml of solution to saturate binding sites in the tubing. This solution will administer one unit of insulin/ hr, if infusion rate is kept 10 ml/ hour or 10 drops/ min by micro drip set (60 drops/ ml). If infusion pump is available, prepare infusion syringe by adding 50 units of insulin to 50 ml of normal saline (1 ml = 1 unit of insulin).

1. Initial rate of insulin infusion and bolus is calculated by measuring the blood glucose and dividing the value by 100 (round off to nearest whole number or 0.5 fraction).
2. Monitor blood glucose hourly and adjust the dose according to above formula.
3. If blood glucose falls >100 mg/ dl or >20% of previous level in the first hour then decrease calculated insulin dose by 0.5 -1.0 unit.
4. If blood glucose does not fall by 50 mg or 10% of previous level within 2 hours of starting insulin infusion, then increase calculated insulin dose by 0.5-1 unit. Maximum limit 50 units/hour.
5. When blood glucose is <100 mg/ dl, stop insulin drip or pump for 60 minutes. Add 5% dextrose @ 75-100ml/ hr. Measure blood glucose after 60 minutes. Restart insulin infusion when blood glucose >100.

Monitoring: Whichever method is adopted, constant monitoring and titration is the cornerstone to achieving good control. Initial monitoring should be hourly till blood glucose level reaches target levels and remains in the range for 3 hours, then 2 hourly till patient is on infusion. If blood glucose levels are within acceptable limits, patient may be considered for changing over to subcutaneous dosing provided oral feeding resumes. Monitoring thereafter can be done at 4-6 points (pre meals, bedtime and on SOS basis to detect hypoglycemia). The aim is to achieve a steady BG level of 140-180 mg/ dl while avoiding hypoglycemia.

Sensitivity to insulin may change rapidly with improvement in the underlying condition and pre emptive 10-20% reduction in infusion rates may be required in these patients [25].

Hypoglycemia: A level of 70 mg/ dl is proposed as cut off for diagnosing hypoglycemia. If symptomatic it should be managed with 50 ml 50% Dextrose intravenously and if asymptomatic give 2-3 teaspoon glucose dissolved in 100 ml water or 200 ml of fruit juice orally. Recheck blood glucose after 15-30 min. Repeat if blood glucose <100 mg/ dl.

Transition to intermediate care: Once the patient improves and starts oral feeding it is time to change over to subcutaneous dosing. The American College of Endocrinology recommends starting with 80% of the prior 24 hour infusion needs with half given as basal and half as prandial dose and a target random blood glucose level of 180 mg/dl [30].

In conclusion, though uncontrolled hyperglycemia clearly predisposes to adverse outcomes, glycemic control continues to be a neglected part of patient management. This is especially so in patients with new onset hyperglycemia. Even in known diabetic patients on treatment, medications are often discontinued or reduced out of fear of causing hypoglycemia.

There continues to be hesitation in using insulin by primary care physicians possibly due to lack of experience. Effective management of hyperglycemia clearly improves clinical outcome. Determining whether aggressive glucose control should be pursued would be governed by factors such as duration of hospitalization, expected course of treatment and survival prospects. However, enthusiasm in striving for lower glycemic levels needs to be tempered by the fact that glycemic variability and hypoglycemia are independent predictors of poor outcome.

Present weight of evidence is in favour of moderate glycemic control in line with findings of NICE-Sugar trial. Upon discharge and recovery from acute illness, patients without known diabetes who had hyperglycemia upon admission or during their hospital stay should be re-evaluated to establish or reject the diagnosis of diabetes mellitus.

Conflicts of Interest

None identified

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