ABSTRACT

Hyperglycemia in critically ill patients is not merely an adaptive phenomenon to stress but it is also associated with increased risk of morbidity & mortality. Various trials conducted since 2001 have consolidated the fact that adequate management of uncontrolled hyperglycemia resulted in better outcome in terms of decreased morbidity, mortality and decreased ICU stay. But this has been diluted by the fact that many recent trials like NICE-SUGAR study that attempted to achieve normoglycemia (80-110mg/dl) have resulted in increased mortality.

Insulin therapy should be initiated in most cases, usually by slow IV infusion. There are various protocols for insulin therapy based on insulin infusions and hourly/2 hourly blood glucose monitoring: none of them have been found to be superior. Moreover, one protocol may not fit for all patients, so other issues like patient’s pre-morbid conditions, individual response to insulin, ICU set up, uniform blood glucose monitoring protocols, availability of trained staffs etc. should be considered before choosing a protocol. Even after completion of NICE-SUGAR and GLUCOcontrol study, the exact target blood glucose level remains debatable but probably it is reasonable to keep blood sugar around 150mg/dl to balance the maximum benefit at the cost of minimum hypoglycemic events, a major concern in tight glucose control.

We need to conduct large, methodologically sound multicenter trials to ascertain which patient populations will benefit most from intensive insulin therapy and to firmly establish the blood glucose concentration at which maximum benefits will be realized. In the mean time a moderate degree of glycemic control maintaining levels mentioned above while avoiding extremes of hypoglycemia and hyperglycemia seems reasonable.

Key words – Hyperglycemia, Hypoglycemia, critically ill patients, insulin infusion therapy

INTRODUCTION

The beginning of the 21st century has witnessed the opening of a new dimension in management of hyperglycemia in critically ill patients, whether diabetic or non diabetic, that was treated with neglectful glycemic control involving haphazard therapeutic approaches (e.g., use of Insulin “sliding scales”) – a practice too common just a decade ago. Though hyperglycemia is a common problem encountered in critically ill patients, it was being ignored as merely an adaptive phenomenon to stress hormones. Recent clinical data since the 1990s have shown that uncontrolled hyperglycemia is associated with poor outcomes in hospitalized patients (Table-1). In addition, post operative glucose levels are a significant predictor of infection rates after cardiac surgery. Various studies conducted since 2004 have shown clearly that use of intensive insulin therapy to maintain tight blood glucose control possibly decreases morbidity and mortality in surgical and medical ICUs (Table 2).

Significant alterations to glucose metabolism occur under conditions of stress such as trauma, burn, major surgery, stroke, acute MI and sepsis. Stress-induced hyperglycemia is the result of increased sympathomimetic activity and increased release of counterregulatory hormones and proinflammatory cytokines. Insulin resistance and insulin secretory capacity in hospitalized patients are affected by numerous factors, including the severity of illness and medications (in particular, glucocorticoids and pressors); in addition, the patient’s diet is often unpredictable in the hospital, and tests and procedures frequently interrupt both meal and medication schedules, further complicating the management of glucose levels. The end result of these physiologic changes is increased endogenous glucose production coupled with insulin resistance that leads to stress-induced hyperglycemia (Figure-1).

Patients receiving dextrose infusions, especially those administered as part of parenteral nutrition are at highest risk for developing hyperglycemia. However, other risk factors predisposing patients to hyperglycemia are: sepsis, organ failure, surgical procedures, pre-existing diabetes mellitus, acute pancreatitis, age and obesity, as well as drugs such as catecholamine vasopressors (e.g., dopamine, norepinephrine), immunosuppressants (e.g., tacrolimus, cyclosporine), and corticosteroids.

EFFECT OF HYPERGLYCEMIA AND INSULIN IN CRITICALLY ILL PATIENTS

Severe hyperglycemia has deleterious effects on vascular, hemodynamic and immune systems, leading to increased susceptibility to infections and increase morbidity and mortality not only in diabetics but also in non-diabetic and newly diagnosed hyperglycemic patients. Whether hyperglycemia is the cause or
Table 1: Clinical Trials In Hyperglycemia Management in Critically Ill Patients

<table>
<thead>
<tr>
<th>Trial Design (year)</th>
<th>Patient Population</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective, nonrandomized, cohort (1998)</td>
<td>Diabetic patients undergoing elective surgery (n=93)</td>
<td>Higher infection rate (except for UTI) in patients with BGL &gt; 220 mg/dl vs BGL &lt; 220 mg/dl on post-operative day 1.</td>
</tr>
<tr>
<td>Prospective, cohort, blinded, case-control (2001)</td>
<td>Patients with known DM, unknown DM, and nondiabetic patients with hyperglycemia undergoing CABG or cardiac valve procedure (n=1044, 300 with known DM, 700 with unknown DM, 44 DM status not mentioned, 74 infected, 970 control)</td>
<td>Frequency of surgical site infections directly and significantly correlated with degree of hyperglycemia during postoperative period. Higher surgical site infection rate in patients with known DM vs patients with unknown DM. Higher surgical site infection rate in patients with known and unknown DM and nondiabetic patients.</td>
</tr>
<tr>
<td>Prospective, randomized, controlled (2001)</td>
<td>Diabetic and nondiabetic surgical ICU patients (n=1548, 765 intensive insulin, 783 conventional insulin)</td>
<td>Lower overall ICU mortality, lower mortality in patients in ICU &gt; 5 days, lower overall in-hospital mortality, lower in-hospital mortality in patients in ICU &gt; 5 days, lower frequency of septicemia, prolonged antibiotics, and bacteremia in intensive vs conventional group.</td>
</tr>
<tr>
<td>Retrospective, cohort (2002)</td>
<td>Diabetic and nondiabetic patients undergoing CABG (n=1090, 400 diabetic, 690 nondiabetic patients)</td>
<td>Diabetic: higher perioperative BGL correlated with higher deep sternal wound infection rate. Higher postoperative infection rate (deep sternal wound infection, donor site infection, UTI) in diabetic vs nondiabetic patients. Higher early mortality in diabetic vs nondiabetic patients.</td>
</tr>
<tr>
<td>Historic cohort (2003)</td>
<td>Diabetic and nondiabetic patients undergoing CABG (n=1574, 545 diabetic, 1029 nondiabetic patients)</td>
<td>Higher overall infection rate in diabetic vs nondiabetics patients. Higher mortality in patients who developed infection in both groups.</td>
</tr>
<tr>
<td>Prospective, one center (2003)</td>
<td>Diabetic and nondiabetic patients admitted to cardiothoracic, cardio-respiratory surgery and medicine ICU (n=523)</td>
<td>In all glucose bands, increased insulin administration corresponded with significantly increased risk of ICU death.</td>
</tr>
<tr>
<td>Retrospective, longitudinal, one center (2003)</td>
<td>Diabetic and nondiabetic patients admitted to general medical, surgical, and coronary ICU (n=1826)</td>
<td>Higher BGL corresponded with higher hospital mortality.</td>
</tr>
<tr>
<td>Nonrandomized, historic control(2004)</td>
<td>Diabetic and nondiabetic surgical and medical ICU patients (n=1600, 800 treatment group)</td>
<td>Lower hospital mortality after protocol implementation. Infection rate similar before and after protocol.</td>
</tr>
</tbody>
</table>

Effect of acute illness is not yet known. It has been shown that intensive insulin therapy exerts its powerful anti-inflammatory effect through its role in functional improvement of insulin sensitive organs through direct anabolic effect in acute illness than promoting tissue repair, decreased free radical production, and enhanced nitrous oxide synthesis, direct anabolic effect on muscles, maintenance of phagocytic function and complement system. [Table.3][19, 20]

Studies pertaining to glycemic control in ICUs (Table 1 & 2)

The earliest landmark trial was done by Van den Berghe et al in surgical ICU patients in 2001, which showed that intensive insulin therapy was associated with a 34% decrease in overall in-hospital mortality. The ICU mortality rate was decreased from 8% to 4.6% (42% reduction). His study demonstrated that tight glycemic control by maintaining blood glucose level below 110 mg/dl can prevent post operative infection, decrease associated complications and reduce morbidity and mortality in critically ill surgical patients. In 2003 Van den Berghe et al demonstrated that even moderate hyperglycemia (110-150 mg/dl) was associated with significant increased in risk of bacteremia. However, trials of tight blood glucose control in medical ICU patients have been less impressive and a trial of blood glucose control in Germany was stopped earlier because of an increased risk of harm (VISEP).

In Van den Berghes’ subsequent trial on 1200 patients in the medical ICU who were predicted to stay for at least 3 days, in-hospital mortality was 37.3% in the intensive-treatment group vs. 40% in the conventional-treatment group; [p=0.33] were not significantly different although complications were less [hospital stay, renal failure] in the intensive-treatment group but the subgroup analyses indicated that the greatest benefit
Unfortunately as there are no definite Vs. 52.5%, p=0.009]. Unfortunately as there are no definite criteria to predict the patient’s stay in ICU at the time of admission, it remains unclear which patient should receive intensive insulin therapy as they enter the ICU.[10]

A meta-analysis of 35 randomized trials by Anastassiou et al in 2004 concluded that insulin therapy in critically ill patients has a beneficial effect on short term mortality in different clinical settings.[21]

The Diabetes Insulin–Glucose Infusion in Acute Myocardial Infarction (DIGAMI) trial on 620 patients with Diabetes mellitus and acute myocardial infarction showed that in the group receiving intensive glycemic management one year mortality was 29% lower than in group receiving conventional glucose control (18.6% versus 26.1%, P=0.03).[21] However the DIGAMI-2 trial remained inconclusive possibly because of inadequate number of patients and inadequate glycemic control even in the tightly controlled group.[26]

Krinsley (2004) studied the effect of intensive management in mixed surgical-medical ICU keeping target glucose level below 140 mg/dl with subcutaneous insulin regimen. Insulin infusion was started only if blood glucose level exceeded 200 mg/dl. The in-hospital mortality rate was significantly lower among patients receiving intensive treatment than among controls (14.8% Vs 20.4%, P=0.002).[9]

The position statement by a panel of American College of Endocrinology (ACE), AACE, and American Diabetes Association (ADA) (2004) [25-26], recommended that a pre prandial target level of 110 mg/dl be set for the plasma glucose level of all hospitalized patients regardless of a prior diagnosis of diabetes. These statements remain controversial, because they extrapolate data from the few trials involving critically ill patients done earlier and are contrary to newer and larger trials like GLUcontrol & NICE-SUGAR study. It is likely that these recommendations will be revised soon.[27]

Inzucchi in 2006 in his review on hyperglycemia management in hospital setting concluded that blood glucose levels should probably be maintained below 140 mg/dl and perhaps below 110 mg/dl. For patients in coronary care unit the reasonable goal may be higher (up to 180 mg/dl) [Fig 2].[27]

In the Glucontrol trial (2007), Perier et al compared the effect of two glucose control regimens by insulin in ICU patients. Patients were randomized to two subsets either with a goal blood sugar of 80-100 mg/dl to 140-180 mg/dl. The goal to enroll 3500 patients had to be terminated prematurely due to occurrence of adverse events [severe hypoglycemia] which was significantly
more frequent in patients with tight blood glucose control group. Perier concluded that tight blood glucose control with a target range of 80-100mg/dl offered no apparent benefit but increased risk of severe hypoglycemia. [28]

Brunkhorst et al (2008) in their VISEP Study found that the use of intensive insulin therapy placed critically ill patients with sepsis at increased risk for serious adverse events related to hypoglycemia without any beneficial effect on patients’ outcome. the mean morning blood glucose level was lower in the intensive-therapy group (112 mg per deciliter [6.2 mmol/l]) than in the conventional-therapy group (151 mg per deciliter [8.4 mmol/l], P<0.001). After the first safety analysis, involving 488 patients, intensive insulin therapy was terminated early by the data and safety monitoring board, owing to an increased number of hypoglycemic events, as compared with conventional insulin therapy. [12]

In the most recently published NICE-SUGAR Study (2009) a multi-centric trial involving 6104 patients ,severe hypoglycemia (blood glucose level, ≤40 mg per deciliter [2.2 mmol per liter]) was reported in 206 of 3016 patients (6.8%) in the intensive-control group and 15 of 3014 (0.5%) in the conventional-control group (P<0.001). There was no significant difference between the two treatment groups in the median number of days in the ICU (P = 0.84) or hospital (P = 0.86). This result confirmed that intensive glucose control, as compared with conventional glucose control, increased the absolute risk of death at 90 days by 2.6 percentage points [27.5 % vs 24.9%]. They have shown that a blood glucose target of <180 mg per deciliter resulted in lower mortality than a target of 81 to 108 mg per deciliter (fig 3). Whether the harm observed in this trial resulted from the reduced blood glucose level, increased administration of insulin, occurrence of hypoglycemia, methodologic factors specific to the trial, or other factors remained unclear. The answer to these important questions must await post hoc analyses of the NICE-SUGAR study. Among questions raised on the credibility of this study are uses of different glomerulometers having wide range of fluctuations and undetected hypoglycemia, early withdrawal of care, excess use of corticosteroids in patients in intensive glucose-control cohort leading to excess mortality. [13] It is therefore likely that moderately intensive glucose control [range of glucose 140-180 mg/dl] may produce better results in critically ill patients than insisting on euglycemia as in the first Van Den Berghe trial.

A more recent meta-analysis involving 26 trials [over 13,000 patients] including NICE-SUGAR data showed no significant benefit of intensive insulin therapy [risk of death 0.93] but a significant risk of hypoglycemia. [29]

Glycemic Control in Critically Ill Patients

**Prevention**

Prevention should be the first step in the management of hyperglycemia. In patients receiving parenteral nutrition, the best approach is to eliminate all other dextrose sources and start with a low dextrose load and advance slowly substituting a portion of the dextrose calories with lipids in parenteral nutrition helps control the hyperglycemia. Normally, 20-30% of total daily calories are provided as lipids.

**Insulin therapy**

- In ICUs/CCUs, continuous intravenous infusion of short acting insulin is the preferred mode of glycemic control as it allows rapid control of hyperglycemia and great flexibility in appropriate dose adjustments (table 4). Several protocols [4, 30-31] are available for insulin therapy in ICU although there is great variability regarding initiation and titration of insulin, bolus dosing and method of insulin protocol adjustments. None of these protocols have been shown to be superior, having their own merits & demerits. One protocol may not suffice for all patients mandating careful selection of protocol. [22] In the light of newer research more liberal target glucose levels may be recommended.

- As the patient’s clinical status improves the transition to...
**Table 4: Algorithm for Insulin Dosing to Achieve Normoglycemia in ICUs [van den Berghe protocol]**

<table>
<thead>
<tr>
<th>Blood Glucose Level (mg/dl)</th>
<th>Action or Adjustment</th>
<th>Frequency of Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>On admission to ICU&lt;br&gt; &lt; 220</td>
<td>Start insulin infusion&lt;br&gt; 2-4 U/hr</td>
<td>Every 1-2 hrs until in normal range</td>
</tr>
<tr>
<td>110-220</td>
<td>Start insulin infusion&lt;br&gt; 1-2 U/hr</td>
<td>Every 1-2 hrs until in normal range</td>
</tr>
<tr>
<td>&lt; 110</td>
<td>Do not start insulin infusion</td>
<td>Every 4 hrs</td>
</tr>
<tr>
<td>During insulin infusion&lt;br&gt; &gt; 140</td>
<td>Increase insulin infusion by 1-2 U/hr</td>
<td>Every 1-2 hrs until in normal range</td>
</tr>
<tr>
<td>110-140</td>
<td>Increase insulin infusion by 0.5-1 U/hr</td>
<td>Every 1-2 hrs until in normal range</td>
</tr>
<tr>
<td>Approaching normal range&lt;br&gt; Normal range&lt;br&gt; 60-80</td>
<td>Adjust insulin dosage by 0.1-0.5 U/hr&lt;br&gt; No change&lt;br&gt; Reduce insulin dosage</td>
<td>Every 1-2 hrs until in normal range&lt;br&gt; Every 4 hrs&lt;br&gt; Recheck within 1 hr</td>
</tr>
<tr>
<td>40-60</td>
<td>Stop insulin infusion, ensure adequate baseline glucose intake</td>
<td>Recheck within 1 hr</td>
</tr>
<tr>
<td>&lt; 40</td>
<td>Stop insulin infusion, ensure adequate baseline glucose intake, administer glucose 10-g intravenous boluses</td>
<td>Recheck within 1 hr</td>
</tr>
<tr>
<td>Steeply falling</td>
<td>Reduce insulin dosage by one half</td>
<td>Every hr</td>
</tr>
</tbody>
</table>

subcutaneous insulin can be made with proper overlap between intravenous and subcutaneous insulin [at least ½-2 hours]. The dose should be adjusted according to latest infusion rate; total daily requirement being divided into basal and prandial insulin dosing [usual ratio 1:1] supplemented if needed by “correction dose” insulin. Sliding scale for insulin therapy should be discouraged because of its tendency to cause wide fluctuations in blood glucose level and very poor glycemic control.[31]

- Similar recommendations apply to hospitalized patients with newly diagnosed hyperglycemia, although some patients may no longer require glucose-lowering therapy after they have recovered from acute illness. Fasting glucose levels (and perhaps glycated hemoglobin values) should be reassessed 1 to 2 months after discharge in these patients, the aim being to confirm [or refute] the diagnosis of diabetes.

**CONTROVERSIES AND UNCERTAINTIES**

While it is generally agreed that adequate glycemic control is an essential part of ICU/critical care, there are still differences among experts among the following points:-

- While various studies conducted since 2001 have suggested that proper management of hyperglycemia improves outcomes, the precise target blood glucose level, optimal mode of administration, type of insulin used and the patients most likely to benefit remains uncertain.[34,35]

- The response to optimal glycemic control immediately to acute myocardial infarction and in septicemic patients is highly erratic. Critically ill patients tolerate hypoglycemia poorly and may remain asymptomatic during periods of severe hypoglycemia.

- The benefits of insulin other than glucose control are also not proven.

- The trial by Van den Berghe in medical ICU patients[2006] [10] and failure of DIGAMI-2 trial to produce a positive result have raised further doubts as to which level of intensive glucose control should be attained in ICU. This has also been the finding of more recent trials[eg NICE-SUGAR, etc]

- Many trials in critically ill patients are single centre, open label trials[possibility of bias?]

- Could insulin itself have direct deleterious effects (sympathetic activation, sodium retention, or mitogenic actions)?

- Did the well-recognized complexities of intensive management of glucose distract from other, ostensibly more important management practices in the ICU?[14-16]

**SUMMARY & CONCLUSIONS**

As recommended by the ADA (2005 &2008)[24,37] based on earlier studies, blood glucose level in ICU patients should be maintained below 150mg/dl and probably even below 110 mg/dl. However NICE-SUGAR STUDY, VISEP and GLUcontrol studies have shown no additional benefit in maintaining blood sugar level below 110mg/dl though post-hoc analysis is needed to validate findings of NICE-SUGAR study in various sub-groups. Intravenous infusion of insulin allows for more rapid titration in critically ill patients and is always recommended for use in ICUs. The optimal glucose target for critically ill patients is not yet ascertained or universally accepted but a reasonable goal may be around 150mg/dl (140-180mg in NICE-SUGAR study).[38]

An ideal protocol that leads to optimal glycemic control without risk of hypoglycemia remains to be ascertained. The approach should be to aim for target glucose level around 150 mg/dl not only to circumvent concerns about hyperglycemia but also to minimize risks of hypoglycemia. The most important part of glycemic management of critically ill patients is proper glycemic control under hospital setting in strict supervision of skilled professionals and trained staff with regular (1-2 hrly) glucose monitoring and adjustment of insulin infusion schedule.

Although the precise glucose targets for ICU patients remain
controversial, having a precise target may be less important than recognizing that -

- Hyperglycemia in critically ill patients whether diabetic or not should be addressed properly.
- Insulin therapy should be proactive, with frequent adjustments to optimize control;
- One should avoid the twin dangers of hypoglycemia and uncontrolled hyperglycemia both of which can have harmful and possibly fatal consequences.

**KEY MESSAGES**

- Uncontrolled hyperglycemia as well as severe hypoglycemia is deleterious and must be avoided.
- Insulin infusion [iv] is required in most patients in ICU with 1-2 hourly glucose monitoring.
- Optimal blood glucose in critically ill patients uncertain - !140-180 mg/dl.
- Step down to basal–prandial-correction dose insulin [sc] when patient improves and oral feeding is possible - no role of “sliding scale” insulin in hospital.
- Patient may or may not require Insulin/OHA after discharge.
- Glycemic targets <110 mg/dl in ICU - More studies needed on which sub-group benefits.

**REFERENCES**