CHAPTER

119

Glycemic Control in I.C.U.

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INTRODUCTION

Hyperglycemia in ICU setting has been a common finding in critically ill patients. Although Diabetes is sometimes the reason for admission to ICU, it is more commonly a co morbid condition complicating the patient management by increasing the severity of primary illness. Also a non-diabetic patient admitted to ICU for a critical illness can have hyperglycemia (also called Stress Hyperglycemia) as a consequence of many factors. Attempts at controlling glycemia have met with conflicting results, probably reflecting an association rather than causality of this marker of stress. The glycemic control in different ICUs whether medical, surgical, or cardiac have different impact in diabetics vs non-diabetics. Hyperglycemia in ICU is associated with increased morbidity, mortality and longer hospital stay regardless of reason for admission (e.g. AMI, Status Post Cardiovascular Surgery, Stroke, Sepsis and Trauma). Stress hyperglycemia is defined as blood sugar level >140 mg% without a previous history of DM or HbA_1C >6.5%.

EPIDEMIOLOGY

The incidence of acute hyperglycemia is difficult to define and may vary from 40-90% depending upon threshold used to define abnormal blood glucose. Hyperglycemia in ICU is associated with poor prognosis in patient with no history of DM. This association is well documented for both admission and mean glucose level during the hospital stay. A review by Deane et al reported 30-40% of patients admitted to ICU suffer from hyperglycemia of whom 10-15% have previously undiagnosed DM. In NICE Sugar Study at least one blood sugar of >180 mg% was recorded in 60% patients without a prior history of diabetes. It is estimated that 15-20% of adult admission to ICU has prior DM and there was suboptimal glycemic control prior to onset of acute illness as shown in a retrospective study that found an HbA1C<6% in only 20% of known diabetic patients. Gornik et al assessed diabetes prevalence 4-6 weeks after discharge from ICU and reported approximately 17% of patients who suffered hyperglycemia during ICU stay actually had unrecognised T2DM. A retrospective review of 614 patients who underwent cardiothoracic surgery hyperglycemia was seen in 80% of patients after surgery. From India Bajwa et al in 2011 reported 38.73% of patients had hyperglycemia (BS >140mg%) on admission to ICU out of which 13.95% had prior history of DM and 4.99% detected diabetic after admission. In a recent prospective study by Godinjak et al 100 patients were followed in a MICU and overall prevalence of hyperglycemia was found to be 54% (35% with DM and 19% with stress hyperglycemia) and 46% were normoglycemic. Patients with stress hyperglycemia had higher mortality (52.6%) compare to patients with previously diagnosed diabetes (48.6%) or normoglycemia (36.9%). Glycemic variability was the strongest predictor of adverse outcome. There was a statistically significant difference in glycemic variability between patients with stress hyperglycemia and normoglycemia. There was no statistically significant difference in length of mechanical ventilation and hospital stay among three group. Patients with stress hyperglycemia had higher mortality than patients with previously diagnosed diabetes or non-diabetics.

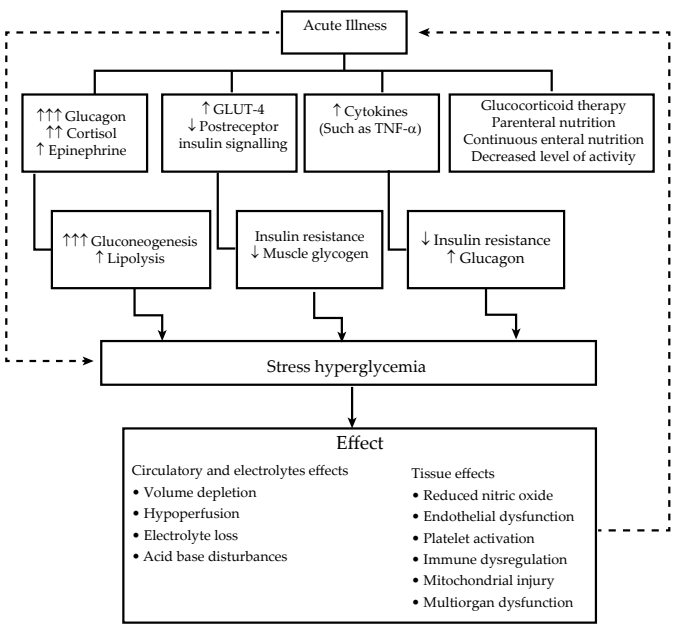

Fig. 1: Pathogenesis of Stress induced Hyperglycemia

PATHOGENESIS

Hyperglycemia may be an independent determinant of prognosis of a critically ill patient or only a marker of dieses severity. The mechanism of development of hyperglycemia in critical illness includes a release of counter-regulatory stress hormones (Corticosteroids, Glucagon, Catecholamine and GH) and pro-inflammatory mediators (TNFα, IL1, IL6). Increased counter-regulatory hormones contribute to alteration in glucose metabolism including increased hepatic glucose production and impaired peripheral utilisation. Catecholamine inhibit insulin release and Cortisol increases hepatic glucose production and stimulates protein catabolism. Pro-inflammatory cytokines not only increase insulin resistance

but also increase hepatic glucose production through Gluconeogenesis. The whole picture is complicated by administration of exogenous corticosteroids, Vasopressors and parenteral solution containing dextrose. The most important contributor to stress hyperglycemia seems to be gluconeogenesis mediated primarily by glucagon and supplemented by cortisol and epinephrine (Figure 1).

BENEFITS OF GLYCEMIC CONTROL (INTENSIVE VS CONVENTIONAL) IN ICU

Till 2006 several randomised controlled trails intensified glucose control with administration of IV insulin both in medical and surgical ICU patients and reported a reduction in multi-organ failure, systemic infection as well as short and long term mortality. In Belgian clinical trial by Vendenberghe et.al, achievement of strict glycemic control (B.S 80-110mg %) by IV insulin therapy in a surgical ICU led to 32% reduction in mortality compared to more flexible glucose control(B.S 180- 215mg%).The same investigators in 2006 conducted a similar trial in a medical ICU and found a reduction in mortality only among patients who stayed in ICU for more than 3days. However, there was no difference in overall mortality in this study and in a sub group of patients staying in ICU for less than 3days mortality was highter in intensive treatment group(H.R:1.09,P=0.05). The NICE sugar trial, the largest randomised controlled trial conducted till date compared two insulin based glucose control strategies (target B,S <180mg% in control group verses a target range of 81-108 mg% in intervention group)in a sample of 6104 patients. In this trial intensive sugar control was associated with increased CV mortality with an absolute difference of 5.8%.A series of meta-analysis, were conducted after NICE sugar trial and found no benefit for intensive control and confirmed that this strategy was associated with increased risk of hypoglycemia. This difference between Vendenberghe and NICE sugar trial is proposed to be due to the amount of energy provided by parenteral nutrition, which was very high in Belgian study indicating greater calorie intake. A meta-regression analysis found that there is a significant relationship between the treatment effect (28 days mortality)and the proportion of calories provided parenterally, suggesting beneficial effect of strict glucose control when parenteral nutrition is energy rich.

A series of trial conducted to ascertain impact of glycemic control in deferent ICU setting and are summarised in Table 1.

When we compare the control between diabetes vs non diabetic hyperglycemia, the later is met with worse outcomes . In a retrospective cohort study, a "U" shaped curve was noted for ICU mortality and mean blood glucose in non diabetics, where as no such relationship was noted for diabetics. All the three domains of sugar control i.e. Hyperglycemia, hypoglycaemia and glycemic variability are affected by premorbid diabetic status of patients. Hyperglycemia was strongly associated with increased mortality in critically ill patients without diabetics than with diabetics. Hypoglycaemia was independently associated with increased mortality in both these population. Increasing glycemic variability may have a stronger association with mortality in non-diabetics than in diabetics.

GLUCOSE MONITERING IN CRITICALLY ILL PATIENTS

Till date capillary blood sugar estimation is the only means available in most of the ICUs in India. In patients receiving IV insulin, hourly blood sugar estimation is done till blood sugar is stable followed by testing every 2 hourly. Patients with or without history of diabetes receiving enteral or parenteral nutrition support should undergo glucose testing every 4 to 6 hours. The testing can be discontinued in a non diabetic patients if glucose values are <140 mg% without insulin therapy for 24 to 48 hours, following achievement of desired caloric intake. Patients on oral feed are measured 4 times a day, before meals and at bed time. More frequent measurements are indicated after a medication change e.g. corticosteroid use, abrupt discontinuation of enteral or parenteral nutrition or in patients with frequent episodes of hypoglycemia.

Since critically ill patients have poor peripheral perfusion, the proportion of glucose reaching periphery is lower. On the contrary there is increased capillary recruitment, increasing the efficiency of capillary glucose uptake. Hence capillary glucose measurements are less representative of arterial and central compartment glucose level.

CGMS is based on a sensor placed in subcutaneous tissue, and is the preferred method for blood glucose measurement in critically ill patients. This method may provide important additional information on trends and fluctuations in glucose control and may predict progression to hyperglycemia or hypoglycaemia.

GLYCEMIC TARGETS

Based on the recent trials, AACE and ADA task force on inpatient glycemic control recommended a blood glucose level between 140-180mg/dl for majority of ICU patients and a lower target between 110-140mg/dl in selected ICU patients (i.e. centres with extensive experience and appropriate nursing support, cardiac surgical patients, patients with stable glycemic control without hypoglycemia). Glucose targets of >180mg/dl and <110mg/dl are not recommended in ICU patients. Based on these recommendations and by adopting a grading systems a consensus recommendation was published in API journal in July 2014. The recommendations by various associations are summarised in Table 2.

INSULIN ADMINISTRATION (IV VS SC)

Indian consensus guideline as well as most of other guideline recommends IV insulin administration as a preferred modality for critically ill patients, because of its rapid onset of action, quicker doses adjustment, better safety profile and predictable glucose lowering effect. Subcutaneous insulin administration (SC insulin) is best avoided in critical care setting, because of its unreliable absorption, unpredictable effects and the "Stacking Effect" causing delayed hypoglycemia. The patient can be shifted to SC insulin once he is stable and started to accept

Table 1: Trils showing Impact of glycemic Control in ICU

Trial, author	Study population, N	Design	Intervention (N. target BG [mg/dl])	Glucose level at endpoint, mg/dl (Mean ± SD)		Mortality (IIT vs. CG)	P-value	Limitations	Hypoglycemia (%)
				IIT	CG				
Trials showing Benefits of IIT vs CG									
DIGAMI 1, Malmberg et al 1995	Diabetic patients with suspected AMI, N=620	Multicentre, randomised	Group 1: GI infusion followed by multi dose SC insulin (n=306, BG:126-198) vs group 2 : ususal care (n=314, BG; not specified)	172.8 ± 59.4	210.6 ± 73.8 mg/dl (P<0.0001)	Infusion group vs CG (18.6% vs 26.1%)	P=0.027	Administration of addition insulin dose to control group patients; small sample size	1.5% vs 0% in 1st 24 h
DIGAMI 2, Malmberg et al 2005	Diabetic patients with suspected AMI, N=12534	Multicentre, prospective randomised, open label	Group 1 GI infusion + insulin – based glucose control (n=474, BG: 126-180); Group 2, GI Infusion + Standard Glucose Control (N=473, BG:126-198); Group 3. Usual care (n=306, BG: not specified	Group 1: 163.8 ± 54.0 Group 2: 163.8 ± 50.4	Group 3: 180 ± 64.8 (P=0.0001)	Group 1 (23.4%); Group 2 (22.6%); Group 3 (19.3%)	Group 1 and 2: P=0.831; Group 2 and 3: P=0.203	Patients in study group 1 did not reach the protocol-outlined glucose levels	
Furnary et al 2003	Surgical ICU, N-=2467	Single central observational	IIT group BG 150-200 mg/dl vs CG BG >200	Daily 178	Daily 188	69% â Deep Sternal Wound Infection	P=0.001		Data not provided
Furnary et al 2006	Surgical ICU, N=3554	Single observational	IIT group, BG 150-200 mg/dl firther down to 100-150 mg/dl vs BG >200 mg/dl	177 +/- 30 mg	213 +/- 41 mg/dl	57% â mortality	P=0.001		Data not provided
Furnary et al 2006	Surgical ICU, N=5534	Single central observational	IIT group BG 150-200 mg/dl firther down to 70-110 mg/dl vs BG >200 mg/dl	Data not provided		65% â Mortality	P=0.001		Data not provided

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Trial, author	Study population, N	Design	Intervention (N. target BG [mg/dl])	Glucose level at endpoint, mg/dl (Mean ± SD)		Mortality (IIT vs. CG)	P-value	Limitations	Hypoglycemia (%)
Leuven 1, Van den Berghe etal 2001	Surgical ICU patients on mechanical ventilation, N=1548	Prospective randomised controlled	IIT group (n=765, BG: 80-100) vs. conventional (n=783, BG: 180-2000	Daily 103± 19	Daily 153 ± 33 (P<0.001)	ICU mortality (4.6% vs 8.0-%); In-hospital mortality (7.2% vs 10.9%)	ICU mortality P<0.04 (adjusted); Hospital mortality P=0.01	Single centre, high use of parenteral dextrose (in TPN)	5 in IG VERSUS 0.8 IN cg
Leuven 2, Van den Berghe et al 2006	Medical ICU, N=767	Prospective randomised controlled	IIT group (n=386, BG: 80-110) vs. CG (n=381, BG: 180-200)	Daily 108±26	Daily 156±25 (P<0.001)	ICU mortality (31.3% vs 38.1%): In-hospital mortality (43.0% vs 52.5%); 90 days mortality (42.2% vs 49.1%)	ICU mortality P=0.05; Hospital mortality:P=0.009 90 days mortality: P=0.06	Single centre, high use of parenteral dextrose (in TPN)	18.1 in IG versus 3.1 in CG
Trials showing no Benefits of IIT vs CG									
VISEP, Brunokhost et al 2008	Patients with sepsis, N=537	Multi centre, randomised open-label	IIT group (n=247, BG: 80-110) vs CG (n=290, BG:180-200)	130 (IQAR 108-167)	138 (QR 111-184) (P=0.05)	28 days mortality (24.7% vs 26.0%); 90 days mortality (39.7% vs 35.4%)	28 mortality: P=0.74; 90 days mortality P=0.31	IIT group did not achieve target; stopped study early for hypoglycemia risk; underpowered	17.0% vs 4.1%, P<0.001
NICE-SUGAR, The NICE-SUGAR innestigators 2009	Medical surgical ICU patients, N=6104	Parallel-group randomised, controlled, computerised treatment algorithm	IIT group (n=3054, BG:81-108) vs CG (nb=3050, BG: 144-180)	115±18	144±23 (P<0.001)	90 days mortality (27.5% vs 24.9%)	P=0.02	IIT group did not achieve target	6.8% vs 0.5%, P<0.001
Glucontrol, Preiser et al. 2009	Medical-surgical ICU patients, N=6104	Prospective randomised multicentr controlled	IIT group (n=536, BG: 80-110) vs CG (n=542, BG: 140-180)	117 (IQR 108-130)	144 (IQR 128-162) (P<0.0001)	ICU mortality (17.2% vs 15.3%): In-hospital mortaltiy (23.3% vs 19.4%); 28 days mortality (18.7% vs 15.3%)	ICU mortality: P=0.41; Hospital mortality: P=0.11; 28 days mortality P=0.14	Stopped study early for hypoglycemia, many protocol violation	8.7% vs. 2.79%, p<0.0001

Abbreviations: ICU: Intensive care unit; IIT Intensive Insulin Therapy; BG: Blood glucose; CG: Conventional Group; GI: Glucose Insulin; TPN: Total Parenteral Nutrition; VISEP: Volume Substitution and Insulin Therapy in Severe Sepsis; DIGAMI: Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction; AMI: Acute Myocardial Infarction; SC: Subcutaneous

Table 2: Recommendations by Associations

Criteria	Consensus	AACE-ADA	API	ACP	CDA	ADS	SSC	AHA
Glycemic target	140-180 mg/dl, <110 mg/dl, is not recommended, 110-140 mg/dl in post-CABG, uncomplicated surgical patients	140-180 tmg/dl, <110 mg/dl is not recommended	140-180 mg/dl in patients with medical morbidity and 110-140 mg/dl for patients with surgical morbidity	140-200 mg/dl, (MICU/SICU patients on insulin therapy)	144-180 mg/dl (MICU/SICU patients), Intraoperative: 99-180 mg/dl (patients with diabetes undergoing CABG) and Perioperative : 90-180 mg/dl for most other surgical patients	<180 mg/dl in patients with hyperglycemia with AMI or acute thrombotic stroke	<180 mg/dl in ICU patients with severe sepsis	90-140 mg/dl in ICU patients with ACS.
Initiating insulin therapy	Initiate IIT (continuous IV insulin infusion when BG level >180 mg/dl; Short-acting regular insulin, preferably with infusion pump; recheck BG before starting IIT in patients without diabetes, start insulin infusion at BG/100U/hour	Initiate IIT (Continuous IV insulin infusion when BG>180 mg/dl	Initiate IIT (continuous IV insulin infusion) when BG>180 mg/dl	Do not use IIT to strickly control or normalize BG in MICU/SICU patients with or without diabetes	Initiate IIT (continuous IV insulin infusion) when BG level >180 mg/dl, other recommendations same as consensus		Initiate IIT (continuous IV insulin infusion when BG level >180 mg/dl	Initiate IIT (continuous IV insulin infusion) when BG level >180 mg/dl
Monitoring of blood glucose	Monitor capillary BG every 1 hour; If BG <70 mg/dl every 20-30 mins till hypoglycemia resolves, restart IIT in modified doses as necessary once BG rises	Frequent glucose monitoring in patients with IV insulin therapy, to minimize the risk of hypoglycemia	Initial monitoring should be done on hourly basis, 2 hourly once BG is stable			Frequent monitoring required in IIT patients	Every 1-2 hrs until BG values and insulin infusion rates are stable, Every 4 hrs thereafter	Close monitoring of BG in ICU patients with ACS

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calories orally. It is recommended to start SC insulin therapy at least 1hr prior to discontinuing IV insulin therapy. When changing from IV to SC insulin it is better to start basal-bolus regimen and dose of insulin should be individualised.

Table 2: Recommendations by Associations

Criteria	Consensus	AACE-ADA	API	ACP	CDA	ADS	SSC	AHA
Transition from IV to SC insulin	Once patient is stable and taking enterl / oral feeds, start transition wherever needed, start SC insulin therapy at least 1 hour prior to discontinuing IV insulin therapy	Once patient is stable and taking enteral / oral feeds, start transition, SC basal 1-2 hr prior to discontinuing IV insuloin	Starts SC insulin atleast 1-2 hr before discontinuing IV insulin or 15-30 min if rapid – acting analoges are used					

Abbreviations: AACE-ADA: American Association of clinical endocrinologiss and American diabetes Associaiton; API: Association of Physicians of India; ACP: American College of Physicians; CDA: Canadian Diabetes Associaiton; ADS: Australian Diabetes Society; SSC: Surviving Sepsis Campaign; AHA: American Heart Association; CABG: Coronary Artery Bypass Grafting; MICU: Medical Intensive Care Unit; SICU: Surgical Intensive Care Unit; AMI: Acute Myocardial Infarction; IIT; Intensive Insulin Therapy; IV: Intravenous; ACS: Acute Coronary Syndrome; SC: Subcutaneous

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