Review Article

Management of Hyperglycaemia in the Hospital Setting

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Abstract

Hyperglycaemia can occur in patients with known or undiagnosed diabetes, or it may occur during acute illness in those with previously normal glucose tolerance (stress Hyperglycaemia). Hyperglycaemia in hospitalized patients is a common problem with serious medical and financial consequences. Hyperglycaemia as well as hypoglycemia has been shown to worsen morbidity and mortality rates in Intensive care unit (ICU) and non-ICU settings. Though tight glucose control has been shown to improve mortality rates in surgical ICU setting, similar results could not be achieved in medical and mixed ICUs. There are no similar large randomized control trials (RCTs) done in general medical and surgical wards. The failure to show good results with intensive therapy is partly attributable to higher frequency of hypoglycemic episodes.

American Diabetes Association- American Association of Clinical Endocrinologists (ADA –AACE) guideline recommends that IV insulin infusion should be used to control Hyperglycaemia in the majority of critically ill patients in the ICU setting, with a starting threshold of no higher than 180 mg/dl (10.0 mmol/l) and the glucose level should be maintained between 140 and 180 mg/dl (7.8 and 10.0 mmol/l). For the non-critically ill patients in the general ward, ADA-AACE guideline suggests a consensus target value of pre-meal glucose below 140 mg/dl and random BG value below 180 mg/dl, preferably using subcutaneous insulin (basal and prandial insulin and a supplemental correctional insulin dose to counter pre-meal Hyperglycaemia). Using standardized protocols in general wards may improve outcomes.

Key-words: Diabetes mellitus, Intensive care unit, Hyperglycaemia, Hypoglycemia, Glucose variability, ICU mortality, Intensive insulin therapy

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Introduction

Hyperglycaemia in hospitalized patients is a common problem with serious medical and financial consequences. In a study done in tertiary care hospitals in South Asian countries including India, hospital admission expenditure for diabetic in patients with no complications ranged from 11 to 75% of per-capita income.[1]

Hyperglycaemia can occur in patients with known or undiagnosed diabetes, or it may occur during acute illness in those with previously normal glucose tolerance (stress Hyperglycaemia). However, irrespective of the cause, Hyperglycaemia is known to be associated with poor outcomes.[2, 3]

This article attempts to present in brief, the data on glycemic control and outcomes in critically ill and non critically ill hospitalized patients, the management of Hyperglycaemia in ICU and non-ICU setting, and general guidelines for transitioning from the critical care units to the regular hospital units and then to home.

Hyperglycaemia and outcome in medical and surgical ICUs

Hyperglycaemia has been noted to be associated with adverse outcomes in both ICUs as well as in general medical and surgical wards. This was illustrated by a retrospective cohort study of 1826 medical and surgical ICU patients. Compared to patients who survived, those who died had significantly higher mean blood glucose levels (172 versus 138 mg/dL), and maximum blood glucose levels (258 versus 177 mg/dL) and analysis of glucose values added predictive power above that achieved by APACHE II scores alone. There was a graded effect, with higher mortality among patients who had higher blood glucose levels. Mortality ranged from 9.6 percent in patients with mean blood glucose between 80 and 99 mg/dL to 42.5 percent in patients with a mean blood glucose greater than 300 mg/dL.[2]

Several randomized control trials (RCTs) have been published evaluating intensive and less stringent glycemic control in medical and surgical ICUs. In one of the landmark RCTs done in surgical ICUs by van den Berghe et al, intensive insulin therapy targeting arterial glucose levels of 80 –110 mg/dl was compared with conventional therapy targeting glucose levels of 180-200 mg/dl among 1500 patients, 13% of them with established diabetes. They achieved mean target glucose levels of 103 vs 153 mg/dl. There was a 42% relative risk reduction in ICU mortality, significantly

lower rates of dialysis and septicemia, as well as a reduced need for blood transfusion and ventilatory support with intensive therapy as compared to conventional therapy.[4] However, in a later study, when the same researchers implemented a similar protocol for glucose control in 1,200 medical ICU patients, they failed to achieve a significant reduction in mortality despite achieving similar mean glucose level as in their previous study in surgical ICU. This unexpected outcome was attributed partly to the 6-fold increase (18.7 vs. 3.1%) in hypoglycemic events (BG <40 mg/dl) in the intensively treated group.[5]

VISEP trial compared conventional with intensive insulin therapy and colloid with crystalloid infusion in ICU patients with severe sepsis. There was no significant decrease in 28-day mortality (24.7% vs 26%) but higher rates of severe hypoglycemia (BG <40 mg/dl) with intensive insulin therapy in patients with severe sepsis (17 vs. 4.1%; P < 0.001).[6] Another study on 504 patients in a mixed medical and surgical ICU showed that intensive glycemic control, achieving similar blood glucose targets as in van den Berghe's study (mean 115 vs 145 mg/dl), did not result in a decrease in morbidity or 28-day mortality (36.6% vs 32.4%), while increasing the rate of hypoglycemia fivefold.[7]

The largest study to date, NICE-SUGAR study, compared tight glycemic control (80-110 mg/dl) with relaxed control (<180 mg/dl) among 6,104 patients in a mixed ICU setting.[8] The 90-day mortality was significantly higher in the intensively treated versus the conventionally treated group (78 more deaths; 27.5 vs. 24.9%; P <0.02) in both surgical and medical patients. Higher mortality risk in intensively treated group persisted when surgical and medical patient subgroups were separately analyzed (OR 1.31 and 1.07, respectively; P=0.10). The intensively treated group had more CV related mortality (76 more deaths; 41.6 vs. 35.8%; P <0.02), as well as incidence of severe hypoglycemia (6.8 vs. 0.5%; P <0.001)[8].

A recent meta-analysis of RCTs reported comparisons between intensive insulin therapy with glycemic targets of 72–126 mg/dl (4.0 –7.0 mmol/l) and less intensive therapy with targets of <150 to 220 mg/dl (<8.3–12.2 mmol/l) among 8,432 critically ill patients. Intensive therapy as compared to conventional therapy, did not significantly improve mortality rate (21.6 vs. 23.3%) or dialysis rate while resulting in a fivefold increase in hypoglycemia (13.7 vs. 2.5%)[9]. There was also no significant difference in mortality when stratified by glucose goal (very tight: < or = 110 mg/dL; or moderately tight: < 150 mg/dL) or by intensive care unit setting - surgical or medical. However a decrease in septicaemia was observed in the intensive therapy group.[9] In a second meta-analysis of 13,567 critically ill patients including NICE-SUGAR data, only patients in surgical ICUs appeared to benefit from intensive insulin therapy (RR 0.63, 95% CI 0.44–0.91); patients in the other ICU settings did not (medical ICU: RR 1.0, 95% CI 0.78–1.28; mixed ICU: RR 0.99, 95% CI 0.86–1.12). But intensive therapy resulted in a sixfold increase in the rate of hypoglycemia in all ICU patients. The different targets of intensive insulin therapy (glucose level ≤ 110 mg/dl or ≤ 150 mg/dl) did not influence either mortality or risk of hypoglycemia.[10]

Hyperglycaemia and outcome in patients with acute myocardial infarction

Diabetic patients with acute myocardial infarction (AMI) have a relatively high mortality rate in the 1st year following the episode. In DIGAMI study, insulin-glucose infusion in the 1st 24 hours followed by multi-dose subcutaneous insulin for ≥ 3 months was s compared to conventional therapy in 620 patients wit h AMI . Ther e wa s 29 % relativ e reductio n i n 1-yea mortality in the infusion group. The subgroup (within insulin infusion group), who had a low cardiovascular risk profile and no previous insulin treatment had an even better mortality reduction (52%).[11] However, DIGAMI 2 study, a multi-centre RCT of 1,253 patients with AMI and diabetes, failed to show a decrease in

Table 1: Major RCTs evaluating intensive insulin therapy in ICU patients #

Study (year) [ref]	n	setting	Mean Glucose level achieved(mg/dl)		Primary outcome	RRR (%)	Odds Ratio (OR)
			Intensive group	Control group			
DIGAMI] (1995)[11]	620	CCU (AMI)	173	211	1 yr mortality	29	NR
Van den bergh et al (2001)[4]	1548	SICU	103	153	ICU mortality	42.00%	0.58 (0.38-0.78)
DIGAMI 2 (2005)[12]	1253	CCU (AMI)	164	180	2 yr mortality	Not significant	NR
Van den bergh et al (2006)[5]	1200	MICU	111	153	hospital mortality	7	0.94 (0.84-1.06)
NICE SUGAR (2009)[8]	6104	Mixed ICU	115	145	90 days mortality	-10.6	1.14 (1.02-1.28)
VISEP (2008)[6]	537	ICU	112	151	28 day mortality	5	0.89 (0.58-1.38)

- Table adapted from Moghissi et al. Diabetes care 2009 [15], NR-not reported

mortality with similar intervention.[12] Another study (Hyperglycaemia Intensive Insulin Infusion in Infarction (HI-5)) showed only improvement in incidence of congestive heart failure and reinfarction at 3 months in the intensively treated group without any significant difference in mortality.[13]

Summary of ICU studies

While the initial study by van den Berghe and colleagues[4] in surgical ICU patients reported remarkable benefit with intensive insulin therapy (target 80-110 mg/dl), consistently positive results could not be achieved in other trials involving medical and mixed ICU patients(Table 1). Actually the largest study published so far showed increased mortality with intensive insulin therapy (NICE-SUGAR). The reasons could be manifold. The positive results reported in the initial studies might be attributable to

1) Differences in measurement and reporting of blood glucose values.
2) Selection of participants (medical ICU, post MI, elective or emergency surgery).
3) Glycaemic variability and fluctuations in an individual patient despite achieving a good average glucose level.[14]
4) Variations in nutritional support between studies.
5) Also some of the later studies had relatively tighter targets even in control group, probably already approaching optimal glucose levels, thus not allowing room for additional improvement with tighter control.

ADA-AACE guideline[15] recommends that insulin infusion should be used to control Hyperglycaemia in the majority of critically ill patients in the ICU setting, with a starting threshold of no higher than 180 mg/dl. Once IV insulin therapy has been initiated, the glucose level should be maintained between 140 and 180 mg/dl. Greater benefit may be realized at the lower end of this range (140-150 mg/dl).[15]

Hyperglycaemia and outcome in non-critically ill subjects

In adult patients admitted to general surgical and medical wards, Hyperglycaemia is associated with prolonged hospital stays, increased rate of infection, disability after hospital discharge, and death.[16, 17] In a retrospective study of 2030 adult patients admitted to a community hospital, mortality was significantly higher in patients with newly diagnosed Hyperglycaemia and those with known diabetes than in those who were normoglycemic (16, 3, and 1.7 %, respectively; P < 0.01) [16]. Hyperglycaemia at admission has also been associated with worse outcomes in patients with community-acquired pneumonia.[17]

Target Glucose levels in non-critically ill subjects

There are no RCTs establishing specific targets for glucose control in the non-critically ill hospitalized patients. ADA/AACE guideline in 2009[15] suggests a consensus target value of pre-meal glucose below 140 mg/dl and random BG value below 180 mg/dl, in general. Modification of the regimen is necessary when BG values are <70 mg/dl. Occasionally, a higher glucose range may be acceptable in terminally ill patients or in patients with severe co-morbidities, as well as when frequent glucose monitoring or close nursing supervision is not feasible.[15]

Treatment Options for achieving optimal glycemic targets

In the hospital setting, insulin therapy is the preferred method for achieving glycemic control in most clinical situations. Insulin inhibits free fatty acids, pro-inflammatory cytokines, adhesion molecules, chemokines and inflammatory growth factors, all of which may be detrimental in critically ill patients. Many of these pro-inflammatory pathways involve the transcriptional factor, nuclear factor-NF-kappa beta (NF-kB). The mechanisms of insulin regulation of these factors are complex, although predominantly insulin seems to have a direct suppressive effect on (NF-kb). Furthermore, insulin enhances nitric oxide synthesis, which promotes vasodilation[18].

Insulin infusion in ICU setting

In the ICU, IV infusion is the preferred route of insulin administration, because the dose can be titrated more rapidly than the dose of oral agents and it does not have a dose ceiling. Also hypoglycemia, if it occurs, is quickly reversible on stopping the infusion. Many protocols have been evaluated and validated for use in critical care setting.[19] Among them, those dynamic protocols which take into account rate of change in glucose levels in choosing insulin infusion rate are better.[20] Frequent monitoring of glucose levels (usually hourly) is needed to minimize the risk of hypoglycemia.

Patients on enteral and parenteral feeding

The glucose levels in patients receiving continuous enteral tube feeding are optimally managed mainly with the use of basal insulin, with correction doses of regular insulin added as needed every 6 hours. A recent study compared sliding-scale regular insulin (SSI) alone or in combination with insulin glargine in patients on enteral nutrition. NPH insulin was added in the 'SSI alone' group if glucose level remained persistently elevated above 180 mg/dl. Though both groups achieved similar mean glucose values (160 mg/dl vs 166 mg/dl, p=0.71), 48% of patients in 'SSI alone' group required the addition of NPH to achieve glycemic targets.[21]

Hyperglycaemia is very common in patients receiving total parenteral nutrition (TPN).[22] In those patients, regular insulin can be added to the intravenous bags; the dose is gradually titrated in increments of 5 to 10 U per litre to achieve glycemic control.

Patients on corticosteroid therapy

Recommended approach is to monitor glucose for at

at least 48 h in all patients receiving high-dose glucocorticoid therapy and to initiate insulin therapy as appropriate.[23] Glucocorticoids can cause marked Hyperglycaemia in the postprandial state. Therefore, these patients frequently require higher prandial doses of insulin than basal doses. During corticosteroid tapers, insulin dosing should be proactively adjusted to avoid hypoglycemia.

Transition from ICU to general ward

Patients who receive IV insulin infusions will usually require transition to subcutaneously administered insulin (SC insulin) when they begin eating regular meals or are transferred to lower-intensity care. Typically, a percentage (usually 70– 80%) of the total daily IV infusion dose is proportionately divided into basal and prandial components (usually 50:50 ratio, unless prandial component needs to be reduced due to poor intake).[24,25] SC insulin must be started 1– 3 h before discontinuation of IV insulin therapy in order to prevent Hyperglycaemia.

Treatment in non-ICU setting

In the general medical and surgical wards, subcutaneous administration of insulin is the preferred method for achieving and maintaining glucose control in patients with diabetes or stress Hyperglycaemia.

However, where resources permit, continuous IV insulin infusion may be used. The preferred subcutaneous insulin regimen for inpatient glycemic management includes two different insulin preparations administered as basal bolus insulin therapy, frequently in combination with a correction (supplemental) insulin scale [Table 2].

The basal component requires administration of an intermediate or long-acting insulin preparation once or twice a day. The bolus or prandial component requires the administration of short- or rapid-acting insulin administered in coordination with meals or nutrient delivery. For patients who are not eating, basal insulin is continued once daily (glargine or detemir) or twice daily [detemir /neutral protamine Hagedorn (NPH)] plus correction doses of a rapid insulin analog (aspart, lispro, glulisine) or regular insulin every 4- to 6-h interval as needed.

Whenever pre-meal glucose level exceeds >140 mg/dl, adjustable supplementary doses ("correction" insulin) of short /rapid acting insulin/analog may be added to the already scheduled prandial insulin. Correction insulin is customized to match the insulin sensitivity for each patient. Most standardized order sets for subcutaneous insulin provide several different correction-dose scales to choose from, depending on the patient's weight or total daily insulin requirement.[26]

Table 2: General guidelines for starting subcutaneous insulin in non-critically ill patients

Hold oral anti-diabetic drugs on admission, if already patient is taking

Starting total daily insulin dose

- 0.4 units/kg of body weight/day when the admission or mean blood glucose concentration is between 140 and 200 mg/dl
- 0.5 units/kg of body weight/day when the admission or mean blood glucose concentration is between 201 and 400 mg/dl
- Lower insulin doses (0.3 units/kg of body weight/day) should be given to elderly patients or those with renal failure (glomerular filtration rate < 60 ml/min)
- Patients already on insulin may be started at the same amount as their outpatient insulin dose, unless decreased intake is expected
- Half of total daily dose will be given as basal insulin and half as rapid-acting insulin.
- Rapid-acting insulin should be given in three equally divided doses before each meal. Hold rapid-acting insulin if a patient is not able to eat

Supplemental doses of rapid-acting insulin are given in addition to the mealtime insulin to correct Hyperglycaemia , selected as per patient's insulin sensitivity (as in table below)

Supplemental Insulin Protocol
BEFORE MEAL. Number of units to be added to scheduled insulin dose
BEDTIME. Give half of supplemental insulin

Blood Glucose (mg/dl)	Insulin sensitive	Usual	Insulin resistant
141-180	2	4	6
181-220	4	6	8
221-260	6	8	10
261-300	8	10	12
301-350	10	12	14
351-400	12	14	16
>400	14	16	18

The basal insulin dose is adjusted depending on the fasting glucose and the overall glucose profile. About 50% of the supplemental dose of insulin given in a day can be incorporated into the basal insulin dose for the next day. Adjustments of prandial insulin doses are based on the level of postprandial glycemia, as reflected by the blood glucose level measured before the midday meal and at bedtime.

Prolonged therapy with Sliding scale Insulin (SSI) as the sole regimen without basal insulin cover is not recommended. It is ineffective in the majority of patients (and may lead to ketoacidosis & hypoglycemia).[27, 28]

As the primary medical problem gets resolved and associated complications such as sepsis improve , glycemic control will improve, necessitating adjusting and tapering the insulin dosage on a day-to-day basis.

Role of oral agents

Oral anti-hyperglycemic agents have a limited role in the inpatient setting and agents like Metformin should be avoided due to the possibility of worsening renal function, hypotension, coexisting sepsis and the possible need for imaging studies with contrast agents. Thiazolidinediones may aggravate fluid overload and precipitate heart failure in some patients. Long acting sulphonylureas should be avoided, where fluctuation in food intake is expected. However, in selected patients, particularly patients who are not critically ill, whose condition is stable, and who are expected to have consistent meal pattern, it is reasonable to continue oral therapies.

Blood glucose monitoring

Patients treated with continuous IV insulin generally require 1 hourly testing initially and later testing frequency can be decreased to every 2h after blood glucose levels become stable. All patients enteral or parenteral nutritional support should undergo glucose testing every 4–6 h. Blood glucose testing can be discontinued in patients without a prior history of diabetes, if glucose values are consistently <140 mg/dL (< 7.8 mmol/L) without insulin therapy for 24–48 h after desired caloric intake is achieved. For patients who are able to eat, glucose measurement is usually performed four times a day: before meals and at bedtime. HbA1c needs to be checked in all patients with Hyperglycaemia (BG>140 mg/dl), especially to guide treatment decisions at the time of discharge.

Discharge Recommendations

Patients with Hyperglycaemia but HbA1C < 6.5% during admission most probably had stress Hyperglycaemia and can usually be discharged without any oral anti-diabetic (OAD) medications. Those who were taking oral anti-hyperglycemic medications and who had a high HbA1c level at the time of admission (suggesting sub-optimal control with oral drugs) should be given a more intensive treatment regime at including shifting to basal insulin plus OADs, or biphasic insulin twice daily or basal-bolus regimens. In those who were newly diagnosed to have diabetes and requiring not more than 20-25 units of insulin per day may be considered for change to oral anti-hyperglycemic drugs. Diabetes education and counselling on Medical Nutrition Therapy (MNT) should be provided to all patients with newly diagnosed diabetes. Outpatient treatment regimen, glucose monitoring techniques and sick-day guidelines should be discussed before discharge.

Areas for further research

Some of the questions needing definitive answers include optimal glycemic targets in non-critically ill patients in medical and surgical wards, optimal glycemic targets in different sub-groups of ICU patients, long-term effects of severe hypoglycemic episodes, effects of glycemic variability during hospital admission and role of continuous glucose-monitoring systems in inpatient settings.

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