Research Article

Title: Hyperglycemia in critically ill patients and its association with increased mortality. A hospital based observational study

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Abstract

Objective: Hyperglycemia is an independent risk factor in critically ill patients, contributing to increased mortality and morbidity. This study was conducted to see the adverse effects of hyperglycemia in the form of increased mortality in medical ICU patients. This Stress induced hyperglycemia is a well known entity and has been found to be associated with adverse outcome in various studies conducted worldwide but the data in India especially in the remote north eastern part is lacking. This will help to predict the prognosis and timely intervention. **Methods**: This descriptive observational study was carried out amongst patients admitted in medical intensive care unit in a tertiary care hospital in Sikkim. Medical records of the patients between July 2015 to December 2015 were reviewed. Patients with admission hyperglycemia (>140 mg %) were chosen for the study irrespective of previous history of diabetes mellitus. Outcome in the form of discharge or death was noted. After fulfilling the inclusion criteria, 160 patients were selected. Chi square test was used to analyze the quantitative data at $p<0.05$ and CI-95%. Results are presented using percentage. **Results**: Patients with admission hyperglycemia (>140 mg %) had significantly higher mortality as compared to patients with normal blood glucose level (p-0.0063, CI-1.347 - 4.936, OR-2.5) This relationship existed both in diabetics as well as new onset hyperglycemics. **Conclusion**: In hospital, hyperglycemia is an independent predictor of mortality in critically ill patients.

Key Words: Hyperglycemia, Mortality, Risk factors, Independent.

Introduction

Any blood glucose level greater than 140 mg/dl (> 7.8 mmol/l) in the hospital setting is defined as hyperglycemia according to American Diabetes Association, 2011[1] and how it leads to adverse effect on patient's outcome is likely multifactorial.

Hyperglycemia due to any cause has been shown to elicit direct vasoconstrictor effects in renal vessels resulting in endothelial dysfunction. Also, it induces an exaggerated inflammatory response resulting in deleterious micro vascular complications that could contribute to increased morbidity and mortality [2]. Increased intracellular glucose levels also activate oxidative stress which is harmful to the endothelium [3]. By increasing circulating concentrations of stress hormones, acute illness can exacerbate hyperglycemia which in turn can exacerbate acute illness by decreasing immune function and increasing oxidative stress [4].

The exact prevalence of hospital hyperglycemia is not known. Observational studies have reported a prevalence of hyperglycemia ranging from 32% to 38% in community hospitals [5, 6] ~80% of cardiac surgery patients in the peri-operative period [7,8] and up to 70% in diabetic patients presenting with acute coronary syndrome[9].

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Hyperglycemia at the time of the admission regardless of diabetes status is an independent risk factor for mortality in intensive care unit (ICU) patients [10].

Acute hyperglycemia produces as much damage as long-standing hyperglycemia. This usually resolves as the acute illness or medico-surgical stress decreases but a small study showed that 60% of patients with admission hyperglycemia had confirmed diabetes at 1 year [11].

Interventional studies have linked the reversal of hyperglycemia with insulin therapy leading to better clinical outcomes in both medical and surgical patients [12]. Studies have clearly found that inpatient hyperglycemia is associated with poor outcomes and that improved glycemic control can result in better clinical outcomes and reduce mortality in certain clinical scenarios.

Materials and Method

This descriptive observational study was conducted in a tertiary care hospital in Gangtok, Sikkim. Study period was 6 months, between June to December 2015. Medical records of the patients admitted in medical intensive care unit were reviewed.

Inclusion criteria: Both male and female patients more than 20 years of age were included. Only those patients in whom random blood glucose was checked at the time of admission were selected. Patients with known diabetes were also included.

Exclusion criteria: Patients with hypoglycemia which itself can cause increased mortality, were excluded. Patients who were discharged against medical advice were also excluded since outcome was not known.

Methodology: Blood glucose level at the time of admission was noted. Prior history of diabetes mellitus and other co morbidities like COPD, IHD, HTN, chronic liver disease were also noted which could have contributed to poor outcome in these patients. Clinical outcome in the form of discharge or death was noted. After strictly adhering to inclusion criteria, total of 160 patients (76 female, 84 males) were selected.

Statistical analysis - Descriptive statistics was calculated using frequency, percentage and proportions. Chi square test was used to analyze the quantitative data at $p<0.05$ and CI-95%.

Results

On reviewing the files of 160 patients, 80 patients were found to be discharged and 80 had expired.

Table 1: Blood sugar level in overall study population in relation to clinical outcome

Random Blood sugar	Expired	discharged	Total patients
Hyperglycemia (>140mg%)	42 (52.5%)	24 (30%)	66
Normoglycemia (<140mg%)	38 (47.5%)	56 (70%)	94
Total patients	80	80	160

p-0.0063 OR-2.579 CI 1.347-4.936

Hyperglycemia, (RBS > 140) at the time of admission was present in 42 (52.5%) expired patients versus 24 (30%) patients who were discharged after being cured (Table 1).

This finding was very significant (p-0.0063). Odds ratio of 2.58 suggested that patients with hyperglycemia were 2.5 times more likely to die as compared to patients with normoglycemia.

Patients with normal blood glucose level were more likely to be discharged.

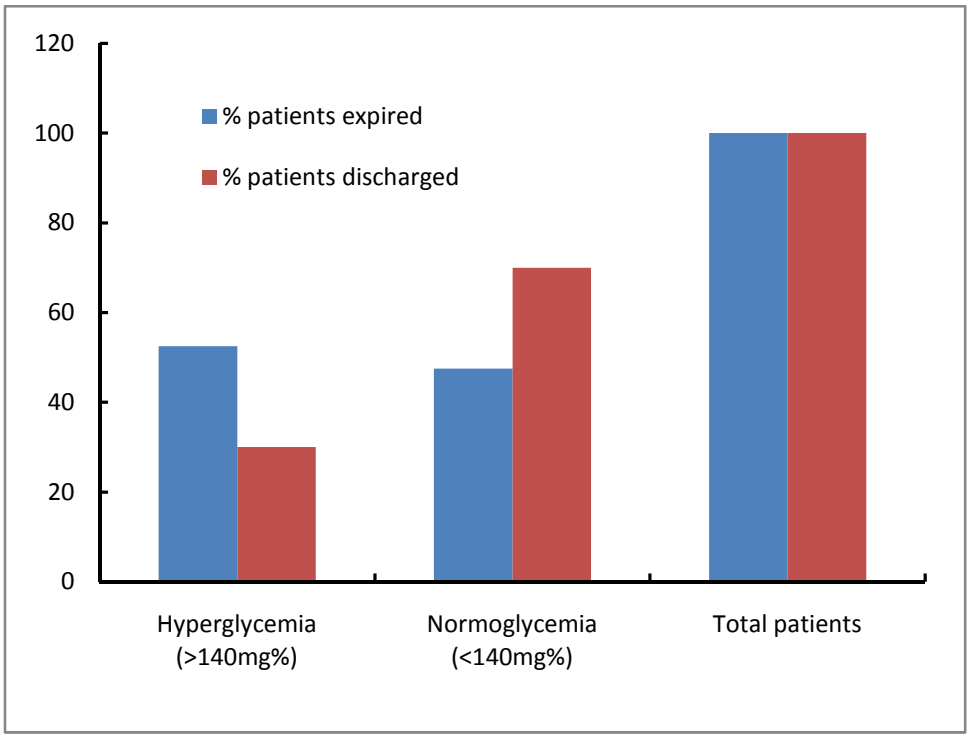

Figure 1. Comparison between patients discharged and patients died.

Table 2: Proportion of patients with new onset hyperglycemia verses known diabetics

Patient with hyperglycemia	66	New hyperglycemia	Known diabetic
Expired	42	26(62%)	16(38%)
Discharged	24	9(38%)	15(62%)

As many as 36 (66%) patients had new onset hyperglycemia out of those 42 patients with hyperglycemia who expired whereas it was present in 9 (38%) patients with hyperglycemia who were discharged (Table 2).

Table 3: Distribution of patients with hyperglycemia in different age groups

Age group (in yrs)	20-39	40-59	60-79	≥80
Expired=42	3(7%)	20(48%)	14(33%)	6(14%)
Discharged=24	4(17%)	9(37%)	6(25%)	5(21%)

Most patients with hyperglycemia both in discharged and expired group were between 40 -80 yrs and sex ratio was almost equal (Table 3 and 4).

Table 4: Sex ratio in patients with hyperglycemia.

Sex	Expired=42	Discharged=24
Male	22(52%)	10(42%)
female	20(48%)	14(58%)

Discussion

Patients with diabetes have a threefold greater chance of hospitalization as compared to those without diabetes [13] but various observational studies conducted worldwide have shown that hyperglycemia was associated with prolonged hospitalization, complications and increased mortality in critically ill, diabetic and non diabetic patients [8,14,15]. Hyperglycemia related adverse outcome was seen even in non critical patients admitted in medical and surgical wards [5, 16, 17]. In our study, we found strong association between in-hospital hyperglycemia and adverse outcome in the form of higher mortality irrespective of presence of diabetes mellitus in patients admitted in ICU [Table 1]. We did not study the mean blood glucose level during the hospital stay which also is associated with adverse outcome according to various studies [18,19]. In a retrospective cohort study, it was found that hyperglycemia in presence of various co morbidities like, COPD, sepsis and cardiac diseases led to increased mortality [19]. In present study, most of the patients with hyperglycemia were more than 40 yrs old [table 3] and co morbidities in the form of hypertension, COPD, sepsis, heart failure, ischemia heart disease and chronic kidney disease were present in almost all of them. Cross-sectional studies have shown higher risk of complications and mortality observed in patients with new onset and stress-induced hyperglycemia compared to those with a known diabetes. In our observation, mortality was higher in new onset hyperglycemia as compared to hyperglycemia in diabetic patients (62% versus 38%) [Table 2].

Hyperglycemia due to any cause has been shown to elicit direct vasoconstrictor effects in renal vessels resulting in endothelial dysfunction. It induces an exaggerated inflammatory response resulting in deleterious micro vascular complications that could contribute to increased morbidity and mortality [2]. Increased intracellular glucose levels also activate oxidative stress initiating a deleterious metabolic cascade of enhanced polyol activity, increase the formation of advanced glycation end products, activation of protein kinase C and nuclear factor kB. Ultimately these responses are harmful to the health of the endothelium [3]. By increasing circulating concentrations of stress hormones, acute illness can exacerbate hyperglycemia which in turn can exacerbate acute illness by decreasing immune function and increasing oxidative stress. This leads to a vicious cycle of worsening illness and poor glucose control [4].

Strict glycemic control can reduce mortality and morbidity in these patients. In a study conducted by Furnary et al (2003), patients with diabetes who underwent coronary artery bypass grafting and were treated with insulin (SCI or CII) were followed and it was found that patients having average blood glucose of 9.8 mmol/L (177 mg/dL) had significantly fewer deep sternal wound infections than patients having average blood glucose of 214 mg/dl. There was reduction in risk-adjusted mortality by 50% [13]. Mortality was higher in patients having blood sugar <200 mg% as compared to ones having blood sugar >200mg% [12]. Patients with hyperglycemia in the setting of acute myocardial infarction also benefitted with insulin therapy. [14] An another study by van den Berghe G et al (2006) showed that intensive insulin therapy to maintain blood glucose at or below 110 mg per deciliter reduces morbidity and mortality among critically ill patients in the surgical intensive care unit [8]. Based on the results of few studies, glycemic target of 80-110 mg% was set in ICU setting [1].

Various RCTs and meta-analyses, however, have shown that low blood glucose target can increase the risk for severe hypoglycemia and mortality without having significant improvement in clinical outcome [20,21,22,23]. Based on the results of recent trials, the American Association of Clinical Endocrinologist (AACE) and American Diabetes Association (ADA) task force on inpatient glycemic control recommended targeting a BG level between 140 and 180 mg/dL for the majority of ICU patients and a lower glucose targets between 110 and 140 mg/dL in selected ICU patients.

Though glucose target cut offs are not clear, it is established beyond doubt that hyperglycemia is associated with poor outcome in critical care settings. According to ADA, any blood glucose level greater than 140 mg% in hospital setting is defined as hyperglycemia so we chose random blood glucose value >140 mg% at the time of admission to study the association between hyperglycemia and increased mortality. This association will help us identify those high risk patients and to decide a blood sugar level above which inventions would be needed to improve outcome and minimize the cost of therapy by reducing the complications and hospital stay in this remote, resource poor, north-eastern state of India. At the same time it might also help to predict development of diabetes in those patients with stress induced

hyperglycemia. We did not study any further hyperglycemia during hospital stay, duration of hospitalization and complications and effect of insulin therapy in outcome in patients with hyperglycemia. More randomized controlled trials and interventional studies are needed for better management and outcome in patients with in-hospital hyperglycemia.

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