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Prevalence and impact of hyperglycemia on hospitalized leukemia patients

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A B S T R A C T

Purpose: Hyperglycemia is a common phenomenon in hospitalized patients and has been associated with poor clinical outcomes. Hyperglycemia was defined as a fasting blood glucose ≥126 mg/dL. In cancer patients' hyperglycemia has been associated with impacting diagnostic imaging studies; facilitating the development of and progression of cancers, and influencing response to treatment. Little is known about the impact of hyperglycemia on clinical outcomes such as: neutropenia, infection and hospital length of stay in hospitalized patients with leukemia. The purpose of this study was to examine the impact of hyperglycemia on the following clinical outcomes: neutropenia, infection and hospital length of stay.
Methods: This retrospective study examined the prevalence and impact of hyperglycemia on clinical outcomes in this vulnerable population.
Results: In this sample of 42 hospitalized patients with leukemia, 60% had at least one incidence of hyperglycemia. Patients with hyperglycemia were 1.6 times more likely ($p < 0.01$) to experience neutropenia than those without hyperglycemia. However, no difference was noted between those with and without hyperglycemia and risk for infection ($p = 0.23$). Hospital length of stay was significantly longer in patients with hyperglycemia (2 days versus 15 days; $p < 0.001$) than those without hyperglycemia.
Conclusions: The findings from this study provide preliminary evidence demonstrating hyperglycemia in the leukemia patient is common and has detrimental effects on clinical outcomes. Understanding the impact of hyperglycemia will inform interventions to mitigate its consequences and improve quality of life for patients with leukemia.

Introduction

Hyperglycemia is a common and serious adverse event occurring in hospitalized patients with or without diabetes. The American Diabetes Association defines hyperglycemia as a fasting blood glucose (FBG) ≥ 126 mg/dL (American Diabetes Association, 2013). Many systemic pathologic processes are induced by the presence of hyperglycemia such as: hyperinsulinemia, insulin resistance, oxidative stress and release of inflammatory cytokines (Buysscharet and Sadikot, 2013). These processes can influence cellular activities and cell signaling pathways (Wang et al., 2012). Because of the potential for these serious consequences the American Diabetes Association (2013) recommends hyperglycemia in the hospitalized patient be promptly identified and treated.

The prevalence of hyperglycemia has been reported in 32% of hospitalized critical and non-critical care adult patients (Swanson et al., 2011). Among patients with hematologic cancers, the prevalence of hyperglycemia has not been well studied. Hammer et al. (2009) found that 99% (1167/1175) of bone marrow transplant (BMT) patients, including patients with leukemia, had a blood glucose ≥ 150 mg/dL during their hospitalization. Only three studies have examined the prevalence of hyperglycemia in leukemia patients, demonstrating that 37–67% of patients incurred hyperglycemia during hospitalization (Weiser et al., 2004; Ali et al., 2007; Matias et al., 2013). Taken together, these studies indicate that hyperglycemia may be a common yet under recognized problem among hospitalized patients with leukemia.

Emerging experimental and clinical evidence suggests that hyperglycemia may impact the outcomes of cancer patients. Researchers have found that hyperglycemia promotes cellular

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changes facilitating the development and progression of cancers (Yi et al., 2012), and response to treatment (Biernacka et al., 2013). Hyperglycemia in the patient with leukemia may be of particular importance as elevations in blood glucose have been shown to weaken the immune system by triggering prolonged expression of proinflammatory cytokines which impairs immune cell signaling (Germenis and Karanikas, 2007). In the presence of hyperglycemia, dysfunction in the activity of the neutrophils (the body's first line of defense against infection) has been noted (Price and Knight, 2009). The intracellular signaling and phagocytic activity of neutrophils has been shown (in vivo) to be negatively affected by elevated glucose (Saiepour et al., 2003). Researchers noted in another in vivo study, when metabolic control of blood glucose was obtained the functions of neutrophils (chemotaxsis, adherence, phagocytosis and bactericidy) were improved (Walrand et al., 2004). The presence of hyperglycemia in patients with leukemia may result in prolonged suppression of the bone marrow and delayed neutrophil recovery placing this vulnerable population at greater risk of life threatening infection and subsequent longer hospital length of stay (HLOS).

A recent literature review conducted by Storey and Von Ah (2012), examined the impact of hyperglycemia on the clinical outcomes in a variety of cancer patients and found eleven studies which linked hyperglycemia to increases in infection, mortality, toxicity and HLOS as well as decreased survival. Subsequently ten additional studies have examined hyperglycemia on at least one of these clinical outcomes (Gebremedhin et al., 2012; Griffith et al., 2011; Jackson et al., 2012; Karnchanasorn et al., 2012; Matias et al., 2013; Pidala et al., 2011; Rentschler et al., 2010; Sheean et al., 2013; Soysal et al., 2012; Villareal-Garza et al., 2012). However, these studies are limited as 12/21 (57%) focused predominately on the BMT population. In fact, only 3/21 (14%) studies were conducted among hospitalized non-BMT leukemia patients. Furthermore, of these studies, only one study examined the impact of hyperglycemia on neutropenia in patients with Acute Lymphocytic Leukemia (ALL) (Weiser et al., 2004). In that study, hyperglycemia (defined as 2 glucose tests $\geq$ 200 mg/dL) was not significantly linked to prolonged neutropenia but was linked to an increase in infection. All three of these studies suggest that hyperglycemia may play a role in infection and mortality in the patient with leukemia (Weiser et al., 2004; Ali et al., 2007; Matias et al., 2013). None of the three studies examined the impact of hyperglycemia on HLOS. The results of these three studies may have been influenced by the varied definitions of hyperglycemia. The American Diabetes Association (2013) considers an FBG $\geq$ 126 mg/dL as clinically significant hyperglycemia which warrants intervention. Our study is the first to examine hyperglycemia as defined by guidelines from the American Diabetes Association (2013) and its impact on significant outcomes (neutropenia, infection and HLOS) in the hospitalized patient with leukemia. Findings from this pilot study will provide data for future hypothesis testing and research regarding the role of hyperglycemia on clinically significant outcomes in cancer.

Therefore, the purpose of this pilot study was to 1) identify the prevalence of hyperglycemia in hospitalized leukemia patients and 2) compare clinical outcomes including, neutropenia, infection, and HLOS in hospitalized leukemia patients with and without hyperglycemia.

Methods

A retrospective cohort study design was used to address the study aims. The study was approved by the institutional review board of a large urban hospital. Sample size was based on the recommendations by Julious (2005) for pilot studies, which takes into consideration feasibility and precision of mean and variance for pilot studies.

Sample and setting

All patients who were hospitalized on the medical oncology unit of a community hospital in the Midwestern United States were potentially eligible. Consecutive leukemia patients hospitalized from October 1, 2009 through February 28, 2011 were identified from the hospital database and screened for inclusion. Patients were included if they had a 1) diagnosis of leukemia, 2) HLOS greater than 24 h, 3) were age 18 years of age or older and 4) had serum FBG laboratory results.

Procedures

Data was abstracted from the medical record on a data collection tool developed for the study. De-identified data was entered into a secured database for analysis. Data was verified for accuracy by randomly selecting 20% of records for review.

Demographic and medical information

The collection tool included demographic data such as: race, age, gender, and body mass index (BMI). Medical information abstracted from the medial record included: leukemia diagnosis, diagnosis of diabetes, laboratory data for FBG, absolute neutrophil count (ANC) and evidence of infection.

For this study hyperglycemia was defined as an FBG $\geq$ 126 mg/dL in accordance with the established guidelines of the American Diabetes Association (2013). Serum FBG values analyzed in the hospital central laboratory were abstracted from the medical record from date of hospital admission to either day of discharge or up to 30 days. FBG's meeting the criteria for hyperglycemia ($\geq$126 mg/dL) were recorded as a dichotomous variable (no/yes) for the analysis.

Outcomes

Clinical outcomes of interest in this study included: neutropenia, presence of infection and HLOS. **Neutropenia**: Neutropenia was defined according to the Infectious Disease Society of America guidelines (2011) as one or more occurrences of an ANC < 500 cells/mm^2. The presence of neutropenia was also noted as a dichotomous variable (no or yes) for analysis. **Infection**: The medical record was reviewed for the presence of documentation of infection by either the physician and/or final laboratory reports and may have included: urinary tract infection, pneumonia, blood stream infection and/or sepsis. The presence of infection was noted as a dichotomous (no/yes) variable for analysis. **HLOS**: HLOS was calculated as the number of days in the hospital from day of admission to either day of discharge or up to 30 days.

Data analysis

Data were analyzed using SPSS version 21. Descriptive statistics were used to describe the sample and determine the prevalence of hyperglycemia. Fishers exact test was used to assess the impact of hyperglycemia on dichotomous outcome variables (neutropenia and infection), and Kaplan Meier was used to examine the relationship between hyperglycemia and HLOS.