ORIGINAL ARTICLES

FREQUENCY OF DRUG INDUCED HYPERGLYCEMIA DURING REMISSION INDUCTION THERAPY IN ADULTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA

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ABSTRACT

Objectives: To determine the frequency of drug induced hyperglycemia during remission induction and its associated risk factors in adult acute lymphoblastic leukemia (ALL) patients.

Study Design: Cross sectional study.

Place and Duration of Study: Combined Military Hospital, Rawalpindi Pakistan, from May 2017 to Nov 2017.

Material and Methods: Fifty one adult patients of newly diagnosed ALL were enrolled in the study. Inclusion criteria included, eighteen years or older, treatment naïve. Patients with history of diabetes, on-going treatment or were taking drugs causing hyperglycemia were excluded from the study. Possible risk factors were recorded including age, body mass index (BMI), gender, family history of diabetes, history of hypertension and disease risk stratification for ALL. Patients were started on standard or augmented Berlin-Frankfurt-Münster (BFM) protocol according to risk category. Fasting and random glucose levels were done twice a week during induction chemotherapy. Hyperglycemia was diagnosed when patients experienced blood glucose greater than 126 mg/dL as fasting or greater than 200mg/dL as post prandial. Data were analyzed using SPSS version 23.

Results: Eighteen of our fifty one enrolled patients (35.3%) experienced hyperglycemia during induction chemotherapy. There was also significant increase in fasting blood sugar levels from baseline readings after induction chemotherapy (p-value<0.001). Univariate analysis demonstrated significant association between fasting high blood sugar after induction chemotherapy with age (p-value <0.001) and BMI (p-value=0.034). While on multivariate analysis only age (p<0.001) was found to have significant association with hyperglycemia.

Conclusion: Hyperglycemia was observed in less than half of our adult ALL patients during induction chemotherapy. Age was a significant risk factor associated with hyperglycemia.

Keywords: Age, Body Mass Index, Hyperglycemia, Lymphoblastic leukemia.

INTRODUCTION

Steroids are an integral part of remission induction therapy in acute lymphoblastic leukemia (ALL) in adults and children. Most of the treatment protocols used to treat pediatric and adult leukemia patients include various steroids like dexamethasone and prednisolone usually in medium to high dosages. Drug induced hyperglycemia is one of the major complications during induction therapy in ALL being treated with steroids and L asparaginase[1,2]. In previous studies its frequency is reported ranging from 10-67% depending on the glucose value considered as hyperglycemia. American diabetes association defines diabetes as having fasting blood glucose greater than 126 mg/dL or post prandial blood glucose greater than 200 mg/dL. Hyperglycemia is associated with poor outcome in adult and pediatric patients of ALL with decreased duration of complete remission (CR)[3]. It leads to increased mortality in critically ill patients as it is a cause of acute complications such as hyperosmolar syndrome and diabetic ketoacidosis[4]. Hyperglycemia is also associated with longer hospital stay, high mortality and morbidity in non-critical adult patients admitted in the hospital[4]. Recent studies have shown that hyperglycemia during induction therapy is associated with higher infectious complications in pediatric patients with ALL, including bacteremia, fungemia and cellulitis, resulting in poorer survival[5]. Hyperglycemia is also linked to leuke-

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mic cell proliferation, as it provides key nutrient for cell growth and proliferation. Tumor cells have altered metabolism with higher glucose uptake and utilization, used for nucleic acid synthesis[6]. Studies have shown that diabetic patients have impaired immunity secondary to decreased production of inflammatory cytokines and interleukins 2, 6 and 10[7]. Hyperglycemia also diminishes the phagocytic and antimicrobial activity of white blood cells. Higher blood glucose levels observed in hyperosmolar syndrome and diabetic ketoacidosis impairs T cell proliferation and response to candida albicans, thereby predisposing to invasive fungal infections[8]. These inflammatory and immune effects of hyperglycemia are particularly important in ALL patients receiving induction chemotherapy as they are more prone to neutropenia and infective complications. Few published data have referred to the epidemiology of treatment-related hyperglycemia in south asian adult patients with ALL. The purpose of the current study was to evaluate the incidence and risk factors of hyperglycemia during the treatment for leukemia among adults in Pakistani population.

MATERIAL AND METHODS

This descriptive cross sectional study with prospective data collection was carried out in the department of oncology, Combined Military Hospital, Rawalpindi from May to November 2017. An attempt was made to analyze the frequency of treatment related hyperglycemia in adult patients of ALL during remission induction and its associated factors. Fifty one patients were enrolled using non-probability purposive sampling technique in the study from Oncology ward, CMH Rawalpindi. All selected patients were newly diagnosed patients of ALL, treatment naïve. Inclusion criteria were: age older than eighteen years, newly diagnosed cases of ALL, euglycemic at diagnosis. Patients who had history of diabetes, receiving steroids or diabetogenic drugs for other diagnosis or were already under treatment for ALL were excluded from the study. Informed written consent was taken from the patients. A detailed history and physical examination was carried out in all selected patients. Blood samples were drawn for baseline complete blood picture, fasting blood glucose, random blood glucose, liver function tests, renal function tests, echo-cardiography, Bone marrow aspiration, trephine with immunopheno typing, cytogenetics and ALL gene markers for stratification of disease. BMI status was divided in four categories, underweight (BMI less than 18.5), normal (BMI 18.5-25), over weight (BMI 25-30), Obese (BMI more than 30). History of hypertension, risk stratification of ALL according to protocol, family history of diabetes, age, gender and lineage of ALL blasts were also recorded as possible risk factors. Age was further categorized into three groups, 18 to 29 years, 30 to 40 years and more than 40 years. Patients with standard risk disease (60.8%) were started on standard Berlin-Frankfurt-Münster (BFM) protocol and those with high risk disease (39.2%) were treated with augmented BFM protocol[9]. Fasting and random glucose levels were done twice a week during induction chemotherapy. Patients were labeled as having hyperglycemia if they had blood glucose level greater than 126 mg/dl as fasting or greater than 200 mg/dl as post prandial on two separate occasions during induction chemotherapy.

Data were entered on computer software SPSS version 23. Quantitative variables like age, baseline glucose levels were measured as mean ± SD. Frequencies and percentages were calculated for qualitative variables like occurrence of hyperglycemia, gender, family history of diabetes, risk group of ALL, BMI, history of hypertension, ALL blast lineage. Linear regression analysis was performed to calculate the association of risk factors with occurrence of hyperglycemia. Effect modifiers like age and gender were controlled by stratification. Post stratification chi-square test was applied and p-value ≤0.05 was considered as significant.

RESULTS

Our study population consisted of fifty one patients of ALL which were given induction

chemotherapy at our hospital. Demographic and clinical characteristics of the study participants are shown in table-I. Median age of our study population was 29 ± 11.99 years (range 18-64) with 31 (60.8%) male and 20 (39.2%) female patients. Of the 51 patients, 14 patients (27.5%) were identified as being overweight while 17 (33.3%) patients had positive family history for diabetes. Patients were characterized into 2 groups based on risk stratification; out which 31 (60.8%) patients were identified as standard risk and 20 patients (39.2%) were categorized as high risk. All of our study population had normal fasting blood sugar at baseline. However, a significant elevated fasting blood sugar was observed in 18 (35.3%) patients on induction therapy (*p*-value <0.001) (fig-I). Age group details are shown in fig-2. Mean fasting blood sugar during induction was 128.12 mg/dl with standard deviation of 34.61. Fourteen patients (93.3%) developed hyperglycemia in age group more than 40 years while 2 (7.6%) and 1 (10%) developed hyperglycemia in age group 18 to 29 and 30 to 40 years respectively (table-II). Similarly 9 (64.2%) and 8 (22.8%) developed hyperglycemia in patients with BMI greater than 25 and in between 18.5 to 24.9 respectively while none developed hyperglycemia with BMI less than 18.5. There was no association observed with gender (*p*-value=0.65), risk group (*p*-value=0.19) and family history of diabetes (*p*-value=0.82) in our study sample. Univariate analysis demonstrated significant association between high fasting blood sugar after induction chemotherapy with respect to age (*p*-value <0.001) and BMI (*p*-value=0.034) (table-II). Multivariate regression model was followed afterwards for investigating association with fasting blood sugar of these significant covariates and significant association was found only with age (*p*-value<0.001) (table-II).

Table-I: Baseline characteristics

Variables	Frequency (%)
Age years; median (range)	29 (18-64)
Male to female ratio	1.6 - 1
Gender	
Male	31 (60.8)
Female	20 (39.2)
Body Mass Index	
Underweight	2 (3.9)
Normal	35 (68.6)
Overweight	14 (27.5)
Family history of diabetes	
Yes	17 (33.3)
No	34 (66.7)
Fasting glucose (After induction)	
<126 mg/dl	33 (64.7)
>126 mg/dl	18 (35.3)
Immunophenotype	
B-cell	42 (82.4)
T-cell	9 (17.6)
Risk group	
Standard Risk	31 (60.8)
High Risk	20 (39.2)

DISCUSSION

In recent years treatment in adult ALL patients has changed, with newer protocols that are inspired from pediatric ALL protocols[9-11]. These protocols have higher doses of non myelosuppressive drugs such as glucocorticoids and L-asparaginase and less use of myelo-supressive

drugs such as anthracyclines. This has resulted in improved outcome and survival in adult ALL patients but has led to increased toxicities associated with glucocorticoids and L-asparaginase[12-14]. Our study included 51 patients of newly diagnosed ALL, who were given induction chemotherapy with BFM protocol. Hyperglycemia was diagnosed when patients experienced blood glucose greater than 126 mg/dl as fasting orgreater than 200 mg/dl as post prandial on two separate occasions. This is in accordance with American diabetes association definition of diabetes. This study showed that 35.3% patients experienced hyperglycemia during induction chemotherapy. These results are similar to international studies. Weiser *et al* (2004) evaluated 278 adult patients with ALL and reported hyperglycemia in 37% of patients being treated with Hyper CVAD regimen. They concluded that patients who experienced hyperglycemia had reduced duration of remission and survival[3]. Similarly, study by Douer *et al* (2014) assessed toxicities of pediatric protocols in adults and in 280 adult patients of acute leukemia during induction chemotherapy and its effect on complicated infections and mortality. They concluded that hyperglycemia significantly increased risk of complicated infections and

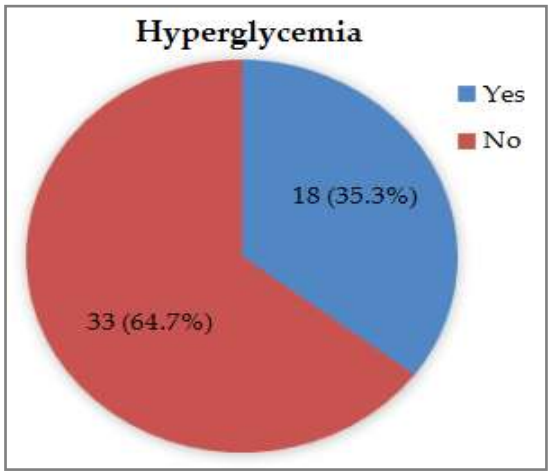

Figure-1: Percentage of patients with hyperglycemia during induction chemotherapy.

mortality during induction chemotherapy[15]. Glucocorticoids and L-asparaginase both are likely causative agents for hyperglycemia and

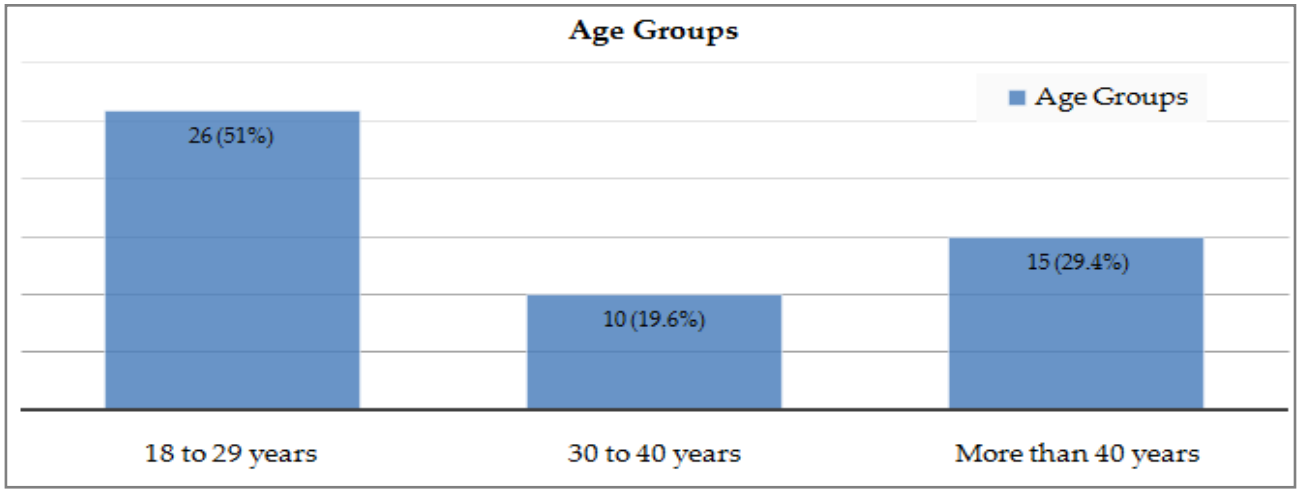

Figure-2: Age groups in study population.

reported 33.3% of patients experienced hyperglycemia during induction[13]. Reduced survival secondary to hyperglycemia is likely attributed to altered metabolism with impaired immune function, increased IGF levels and proliferation of leukemic cells, leading to early relapse[15]. Matias *et al* (2012) studied prevalence of hyperglycemia exert their effect through different mechanisms. Glucocorticoids cause dose dependent hyperglycemia by increasing insulin resistance, decreased uptake of glucose by muscles and adipose tissues (by blocking insulin sensitive glucose transporter 4), increased breakdown of adipose and muscle tissue, inhibition of insulin

secretion, increased glucose output by hepatic gluconeogenesis and increasing free fatty acids and triglyceride production. It causes peak plasma glucose levels 6-8 hours after administration. L-asparaginase causes hyperglycemia through reduced secretion of insulin by Beta cells in pancreas. Douer *et al* (2014) studied use of asparaginase in adult ALL patients and its associated toxicities. Major toxicities (grade 3/4) reported were transaminitis (67%), hyperglycemia (33%), hyperbilirubinemia (31.3%), hypertriglyceridemia (17.6%) and other minor adverse effects. Studies have shown that glucocorticoids and L-asparaginase in combination cause greater degree of hyperglycemia as compared to using alone[5]. Acute stress secondary to infection, disease process and pain also exacerbates hyperglycemia during hospitalization. This study showed that age (p<0.001) and BMI status (p=0.034) were significant risk factors associated with hyperglycemia using uni-variate analysis. While on multivariate analysis, age was the only factor with significant association. Patients above 40 years of age had much higher frequency of hyperglycemia as compared to lower age groups. Gonzalez-Gonzalez *et al* (2013) and others have shown similar results, where majority of the patients who experienced hyperglycemia during induction chemotherapy were of higher age group[1,3,16]. Lee and colleagues (2014) studied effects of glucocorticoids in non-Hodgkin's lymphomapatients with CHOP chemotherapy. They concluded that risk factors including age greater than 60 years and BMI greater than 30kg/m^2 were significantly associated with glucocorticoid induced hyperglycemia[17]. Hough *et al* (2015) studied efficacy and toxicities of pediatric inspired chemotherapy in teenagers and young adult ALL patients. They concluded age as a significant risk factor for increased toxicities. Major toxicities in higher age group included hyperglycemia pancreatitis, bacterial infection, methotrexate encephalopathy and mucositis[14]. Older age and obesity are well known risk factors for development of diabetes mellitus. Both risk factors are associated with increase insulin resistance and reduced peripheral uptake of glucose. Older patients also have lower pancreatic reserve which predisposes them to hyperglycemia. Although most of the drug induced hyperglycemic events are transient and settle once the medication is stopped, but there is significant risk of complications like infections, ketoacidosis and hyperosmolar coma secondary to severe hyper-

Table-II: Chi square test and linear regression to study association of independent variables with hyperglycemia during induction chemotherapy

Independent Variables	Explanatory Variable	Fasting Sugar >126 mg/dl		Chi Square Test	Regression Analysis	
		Yes	No		Univariate	Multivariate
				p-value	*p*-value	*p*-value
Gender	Male	11	20	0.684	0.685	ND
	Female	6	14			
Risk Group	Standard Risk	10	21	0.840	0.839	ND
	High Risk	7	13			
Family History of diabetes	Yes	5	12	0.673	0.675	ND
	No	12	22			
Age	18 to 29 years	2	24	<0.001	<0.001	<0.001
	30 to 40 years	1	9			
	More than 40 years	14	1			
Body Mass Index	Underweight	0	2	0.011	0.034	0.328
	Normal	8	27			
	Overweight	9	5			

ND: not determined

glycemia, thereby increasing the mortality rate in such patients[15]. Medication induced hyperglycemia is usually controlled by insulin as it provides greater control of blood glucose. Strict control of hyperglycemia is not recommended as it can cause iatrogenic hypoglycemia and increase mortality[18]. Recent studies have suggested use of metformin and other oral hypoglycemic drugs for control of hyperglycemia during ALL treatment. Khanh Vu and colleagues (2012) studied use of intensive insulin regimen for hyperglycemia during ALL induction as compared to oral hypoglycemic drugs. They concluded that exogenous insulin administration was associated with lower remission duration, progression free survival and overall survival. While metformin and thiazolidinediones were associated with improved survival in ALL patients[18]. These drugs are considered a safer alternative to insulin for drug induced hyperglycemia as it is less likely to cause hypoglycemia. Metformin and thiazolidinedione PPARγ ligands enhance daunorubicin induced apoptosis. They cause activation of AMPK leading to inhibition of AKT/mTOR signaling pathway in leukemic cells. Oral hypoglycemics also inhibit tumor angiogenesis and invasion and hence block leukemic proliferation[19]. Use of metformin and thiazolidinediones has been suggested to improve survival in hyperglycemic ALL patients, while insulin and analogs increases chemo-resistance through different mechanisms[20,21]. Mild to moderate hyperglycemia can be treated with oral drugs such as metformin and thiozolidinediones while severe hyperglycemia can only be managed by insulin therapy with a combination of a short and long acting insulin. This provides immediate effect with greater control and frequent dose changes according to patient requirement.

CONCLUSION

Hyperglycemia was observed in less than half of our adult ALL patients during induction chemotherapy with BFM protocol. Age was a significant risk factor associated with hyperglycemia.

RECOMMENDATIONS

During treatment with chemotherapeutic drugs and steroids, frequent blood glucose monitoring should be done. Diabetic patients using insulin or oral hypoglycemic drugs should have their glycemic control optimized before starting chemotherapeutic drugs. Hyperglycemia and its related complications should be actively managed to reduce mortality and morbidity during induction chemotherapy.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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