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The incidence of hyperglycemia during the induction phase of chemotherapy in patients with acute lymphoblastic leukemia

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Abstract
Background: Hyperglycemia is one of the most complications of corticosteroid and asparaginase during induction phase of chemotherapy in children suffering from acute lymphoblastic leukemia (ALL).
This study was carried out to evaluate the incidence of hyperglycemia and associated risk factors during chemotherapy induction phase at Amirkola Children's Hospital.
Materials and Methods: In this cross-sectional (retrospective) study, 150 children (mean age: 79.16±42.68 months) with ALL were evaluated (2000- 2011). Hyperglycemia was described as random blood glucose level more than 200mg/dl in patients less than 2 years old. In patients older than 2 years, fasting blood glucose level more than 110-125 mg/dl was considered as impaired glucose level and fasting blood glucose level more than 126 mg/dl was defined as diabetes mellitus. The data were analyzed using SPSS (version 18) and running chi square test, pearson Ccorrelation, and logistic regression. P-values less than0.05 was considered statistically significant.
Results: Out of 150 children with ALL, 21 (14%) of them had hyperglycemia, but none of them had diabetic ketoacidosis. Hyperglycemia was significantly associated with gender (P=0.014) and age. (P=0.000) which was more likely in patients older than 10 years. The incidence of hyperglycemia was also related to BMI (P=0.000). Relapse rate for ALL was 14.7%, which was not significantly associated with hyperglycemia.
Conclusion: Hyperglycemia was common and transient during induction phase of chemotherapy and it was correlated with age, sex, and weight.
Key words: Acute Lymphoblastic Leukemia, Hyperglycemia, Induction Chemotherapy

Introduction

Acute lymphoblastic leukemia (ALL) is the most prevalent cancer in children, (including 25%) younger than 15 years (1). It's an aggressive neoplasia with uncontrolled proliferation of aberrant lymphocytes (2). Due to antilekemic profiles cuased by rgeting antigens on the lymphoblast cell surface, its suggested uses these agents alone or in combination with chemotherapy to improve outcomes in relapsed or refractory status of disease (3).Since the prevelance of ALL survivors in childrenis increasing, attentions are focused on the long-term effects of ALL and minor toxic effects in pharmacological treatments (4, 5). Studies demonstrated that chemotherapy in children with ALL can cause short and long term effects and alterations. It was observed that, after a corticosteroid therapy, some ALL survivors experienced obesity or metabolic disorders especially after treatment with dexamethasone and prednisone (4). Other

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significant late effects are obesity, dyslipidemia, hyperlipidemia, and diabetes mellitus (2). Hyperglycemia occurs during chemotherapy of patients suffering from ALL (6-9) with an incidence rate of 10% (6,7), caused by administration of asparaginase and corticosteroids (10-13). In the most cases, hyperglycemia recover upon cessation of corticosteroid-asparaginase and almost no long-term hyperglycemia is observed in these patients (8, 9, 14) Accurate assessment and early treatment are important in the prevention of Diabetic Ketoacidosis (DKA) and Nonketotic Hyperosmolar Coma (6). Factors such as age, sex, and weight can affect the incidence of hyperglycemia (6,8). Risk of hyperglycemia in patients more than 10 years is relatively high (8), probably due to increased insulin resistance resulting from gonadal steroids increased during puberty (6). Previous studies revealed Transient Hyperglycemia (TH) may happen in 4–15% of pediatric ALL patients (12, 15). These studies demonstrated that age>10 years, obesity, family history of diabetes, and Down syndrome were risk factors for the emersion of TH. While TH spontaneously obviates in almost all patients after induction therapy, 39–75% of children with TH need insulin therapy (12), and few of them develope diabetic ketoacidosis (8). Hyperglycemia, in the induction phase of therapy, may increase the risk of serious infections, mortality, and disease recurrence in patients with ALL (6). Approximately, 20% to 25% of children with ALL who achieve remission following induction therapy are subsequently relapsed (9). Mostly, early relapse occurrs in the first 18 months of treatment, intermediate relapse happens between 18-36 months from treatment, and late relapse occurrs after 36 months chemotherapy (16, 17). Regarding the occurrence of hyperglycemia during the induction phase of chemotherapy for ALL patients, the risk of DKA following hyperglycemia, which is life threatening, and reported recurrences of ALL, we intended to investigate the prevalence of TH in ALL patients during chemotherapy.

Materials and Methods

This cross-sectional (retrospective) study was conducted on all of the ALL patients admitted to the hematology ward of Amirkola children's hospital, Babol, Iran, from 2000 to 2011. We included patients who admitted for the first time with ALL diagnosis and asparaginase and/or corticosteroid were prescribed for them. The exclusion criteria were previous history of diabetes mellitus, death during induction chemotherapy and incomplete record information on their files.

All included patients were analyzed at the first 4 weeks of treatment for hyperglycemia during the induction phase of chemotherapy. The onset of drugs and the appropriate dose of drugs for the induction phase of chemotherapy are presented in Table I.

We identified two categories for relapse, namely clinical and laboratory, Clinical relapse was defined as recurrence of some signs and symptoms, including fever, bone pain, hepatosplenomegaly, and lymphadenopathy. Laboratory relapse referred to presentation of full blood count abnormality and presence of more than 5% blast in bone marrow cells.

In children under 2 years old, who could not tolerate 8-hours fasting, hyperglycemia was defined by 200 mg per deciliter (mg/dl) or more glucose blood level in two times venous blood sampling. In children more than 2 years old, hyperglycemia was defined based onthe standard criteria defined by Dinner et al's study. Blood glucose was measured by 1 cc sample of venous blood and a diagnostic kit (Pars Azmoon Co., Tehran, Iran) through glucose oxidase method.

Blood glucose was measured before initiation of treatment, once a week during 4 weeks of induction therapy, and also at any time during treatment when symptoms of polyuria and polydipsia were observed.

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After confirmation of hyperglycemia and according to the patient's consciousness and arterial blood gas (ABG) results, we evluated the occurrence of DKA and its stages. Capillary blood glucose was also measured in patients with hyperglycemia every 6 hours, using Accu-Chek Active® glucometer (purchased from Germany). Insulin therapy was not planned for patients with gradual decline in blood glucose levels, while subcutaneous regular insulin therapy program was done for those who had persistent and uncontrolled high blood glucose levels, and they were followed when insulin therapy was discontinued. To investigate the relationship between hyperglycemia and age, patients were divided into different age groups, including under 5 years, 5-10 years, and over 10 years old. In this study, patients' weight and height were obtained and BMI of patients was calculated using Weight/Height formula. Accordingly, patients were classified into 4 categories, namely lean (below the 5th percentile), normal (between the 5th and 85th percentile), overweight (between the 85th and 95th percentile), and obese (at/above the 9th percentile) (3). Then, the relationship between hyperglycemia and BMI was assessed. The protocol of this study was approved by Ethic Committee of Babol University of Medical Sciences, Iran (NO: MUBABOL.REC.1391.3).

Statistical analysis

Data were analyzed using SPSS (version 18) and running chi-square, t-test, pearson's correlation coefficient, and logistic regression. P-value<0.05 was considered statistically significant.

Results

One hundred fifty patients with ALL were selected from October 2001 to October 2011. The mean age of patients was 79.16±42.68 months. Twenty-one (14%) patients had hyperglycemia, of which 7 patients (33.3%) had glucose intolerance and 14 patients (66.7%) had diabetes mellitus (Table 2). Incidence of hyperglycemia were 6.9% (5 patients) in female and 20.5% (16 patients) in male (p=0.014). Two patients were treated with subcutaneous insulin injection, which was discontinued after induction phase of chemotherapy. Blood sugar in other 19 patients gradually declined and they did not require any treatment (Table 3).None of the patients had DKA. The most common onset of hyperglycemia was the second week and then the first week during chemotherapy induction phase. As shown in Table 4, hyperglycemia was observed in 20.5% of male patients and in 6.9% of female patients, revealing a significant relationship between gender and hyperglycemia (P-value=0.014). Among patients with hyperglycemia, 4.8% were younger than 5 years, 38.1% were 5-10 years, and 57.1% were older than 10 years. According to chi-square test, a significant association between hyperglycemia and age was observed (P-value=0.000). According to results, 47.6% of patients with hyperglycemia were located at 5th-85th, 28.6% at 85th–95th and 23.8% of patients at/above 95th BMI percentile, suggesting that more than half of patients with hyperglycemia were located at/above 85th BMI percentile. Having runned chi-square test, a significant association between hyperglycemia and BMI was observed (P-value = 0.000). Relapse of ALL for pediatric patients was 14.7%, while its occurrence was 9.1% in hyperglycemia cases but 90.9% in cases without hyperglycemia. Therefore, according to the chi-square test, there was no significant relationship between relapse and hyperglycemia. (P-value = 0.370).

Using logistic regression, the effect of three factors, namely sex, age, and weight on hyperglycemia were investigated according to BMI and the following results were obtained (Table 4).

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Table I.Guide on the chemotherapy regimen used for induction phase

Phase	Treatment / drug dose
Induction	Prednisone: 60 mg/m² per day Dexamethasone: 6 mg/m² per day up to 28 days of treatment L-asparaginase: intramuscular, 6000 unit/m², from fourth day, per week 3 times to 9 doses Vincristine: intravenous, 1.5 mg/m² in Days 0,7,14,21 Methotrexate and cytarabine: intrathecal, once a week

Table II: General Findings of this study

Requiring insulin treatment	Type of hyperglycemia			Patients with hyperglycemia	The total number of patients 150 persons	
	DKA	Diabetes	Glucose intolerance		Female	Male
2 patients	0%	14 (66.7%)	7 (33.33%)	21 (14%)	72(48%)	78 (52%)

Table III: Time of hyperglycemia, from the beginning of the treatment on the basis of week

Week	The number of patients	The percentage of patients
1st	9	42.9%
2nd	10	47.6%
3rd	2	9.5%
4th	0	0%

Table IV: Risk factors of hyperglycemia in patients with ALL (logistic regression)

	Percent of hyperglycemia	Odds ratio * CI95%	P-value
All patients n=150	14%(21)	—	—
Gender			
Female	6.9%(5)	6.178	0.008
Male	20.5%(16)	1.625-23.478	
Age (years)			
≤5	1.4%(1)	5.41	0.000
5-10	15.7%(8)	2.239-13.101	
10≤	41.4%(12)		
BMI (%)			
≤5	0%		
5-85	8.8%(10)	3.508	0.003
85-95	42.9%(6)	1.548-7.954	
95≤	55.6% (5)		

CI, Confidence interval

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Discussion

Transient hyperglycemia commonly occurs during chemotherapy in adults and children suffering from ALL. This study demonstrated that 14% (21 patients) out of 150 cases experienced hyperglycemia in induction phase of chemotherapy. However, Lowas et al., conducted a retrospective study in 2009 on 162 ALL patients with who aged 2-18 years old, and revealed that 20.4% of these patients experienced hyperglycemia (8). The higher percentage of hyperglycemia in Lowas et al., study could be due to higher age average (2-18 years) compared to that in our study. Baillargeon et al., reported incidence of hyperglycemia in 17.5% of females that was higher than males (7.1%) (6), but in our study, from 21 (14%) cases suffered hyperglycemia, 20.5% (16 cases) of them were male and 6.9% (5 cases) of them were female. However, no difference in the incidence of hyperglycemia was observed by sex in Lowas et al.'s study (8), but, incidence of hyperglycemia was significant difference in our study. In this study, the incidence of hyperglycemia increased with age, so that 57.1% of patients with hyperglycemia were more than 10 years, 38.1% cases were 5-10 years, and 4.8% were under the age of 5 years. In line with the findings of the present study, Lowas et al., reported incidence of hyperglycemia in patients older than 10 years (8). Baillargeon et al., also achieved the same result for the patients aged 13-18 years old (6). It seems that the incidence of hyperglycemia in the older age group may be related to higher secretion of gonadal steroids. Similar to our findings, Lowas et al., and Baillargeon et al., documented the higher incidence of hyperglycemia in patients with BMI above 85th percentile. This finding might be due to higher insulin resistance caused by overweight (6, 8). No patient in this study was diagnosed with DKA, while in the Roberson et al.'s study, 6 ones out of 797 patients were diagnosed with DKA, among which four were ≥10 years (18). This finding can be due to the accurate control of patients during onset of hyperglycemia as well as the lower number of patients compared to that in Roberson's research.

In this study, the most common onset of hyperglycemia was the second week of induction chemotherapy with 47.6% followed by 42.9% in the first week. Significant correlations were observed between the incidence of hyperglycemia and age, gender, and BMI according to logistic regression analysis. Lowas et al., reported significant correlations between the incidence of hyperglycemia and age and BMI using logistic regressions, but non between the incidence of hyperglycemia and gender (8). Considering the relapse rate of ALL, it was 14.7% in the present study, 20% in a study conducted by Hazar et al., in Turkey (19), and 20-25% in Szczepanek's study (20). No significant correlation was found between onset of hyperglycemia and relapse of the disease in this study, but Weiser et al. demonstrated that hyperglycemia was a risk factor for the early relapse of ALL. Moreover, patients with impaired blood glucose were 1.57 times more likely to progress to relapse than those with normal blood glucose (21). The results of this study suggested that the incidence of hyperglycemia in children with ALL was relatively common in the induction phase of chemotherapy. In almost all cases, it was transient, and it only required treatment with insulin in very few cases. As a result, the accurate analysis of blood glucose during treatment seems reasonable.

Conclusion

Hyperglycemia is common and transient during induction phase of chemotherapy and it can associate with sex.

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Conflict of interest

Authors declared no conflict of interst.

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