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Frequency and Risk Factors for Hyperglycemia in Children with Acute Lymphoblastic Leukemia During Induction Chemotherapy

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Abstract

Back ground: *Hyperglycemia is a common side effect and it has long been recognized as a consequence of corticosteroids and L-asparaginase, chemotherapeutic agents key to ALL treatment. This study was done to determine the frequency and identify the risk factors for hyperglycemia in paediatric ALL during induction chemotherapy.*

Material & Methods: *This prospective observational study was done among 87 newly diagnosed ALL cases of 1-18 years of age. After initial work up patient got induction chemotherapy according to UK ALL 2003 (modified) protocol in BSMMU. Anthropometric measurements and CBC, RBS/ 2 hours after glucose/ FBS and corresponding urine sugar was assessed after 2nd, 4th, 6th and 9th dose of L-asparaginase and after completion of induction. Data were analyzed by SPSS 17.0.*

Results: *Eight patients (9.75%) of the study cohort developed hyperglycemia. Among ≥10 years of age 36.8% had hyperglycemia compared to 1.6% of younger children (p<0.001). No gender difference was found. Obese and overweight (p <0.001 in both cases), positive family history of diabetes mellitus using 4 drugs during induction remission phase of chemotherapy were found significant risk factors for hyperglycemia.*

Conclusion: *In this study frequency of hyperglycemia was 9.75% and frequency of transient hyperglycemia (TH) was 7.3%. Older age, obese or overweight children, positive family history of diabetes mellitus, patient getting regimen B according to UK-ALL 2003 (modified) protocol had shown increase the risk of hyperglycemia.*

Key words*: Acute lymphoblastic leukemia (ALL), Induction Chemotherapy, Hyperglycemia, Risk factors.*

Introduction

Acute lymphoblastic leukemia (ALL) is the most common malignancy of childhood accounting for 25% of all childhood cancers.[1] Childhood ALL is also common in Bangladesh. In 2012 at department of Paediatric Haematology and Oncology, BSMMU, 58% cases of ALL among 455 newly diagnosed children with malignancy were recorded.[2] The superior outcome achieved in childhood ALL has been attributed to a higher proportion of favorable genetic subtypes, more effective treatment options and better compliance with treatment by patients, parents and doctors.[3] Despite significant advancements in survival long term complications in childhood cancer survivors, such as growth impairment or endocrine dysfunction are well known and these complications are not only related to chemotherapy and/or radiotherapy but also determined by individual host characteristics. Hyperglycemic hyperosmolar non-ketotic syndrome and diabetic ketoacidosis, life threatening acute complications have been rarely reported as adverse effects in children during ALL induction chemotherapy.[4-6] In contrast, hyperglycemia for a short period has been described as a common event during ALL induction chemotherapy in both adults and children and still remains a complication that is not well understood.[7,8]

Hyperglycemia has long been recognized as a consequence of corticosteroids (either prednisone or dexamethasone) and asparaginase, chemotherapeutic agents key to ALL treatment. These medications are usually administered concurrently in high doses during the initial induction phase of chemotherapy. As a result, hyperglycemia frequently develops during this

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phase, with resolution after the steroids and asparaginase have been discontinued or reduced in dose.[8-12] This phenomenon has been referred to as transient hyperglycemia (TH).[4] In ALL, potential factors triggering hyperglycemia include direct infiltration of the pancreas by leukemic cells, beta cell dysfunction induced by chemotherapeutic agents such as L-asparaginase, and increased insulin resistance and hepatic gluconeogenesis secondary to glucocorticoids.[6,13] In Bangladeshi study hyperglycemia was documented among 8% of acases.[14] In different studies from abroad that was found in 4–20% of pediatric ALL patients.[8,10,11] Those study have identified age >10 years, high initial leukocyte count, obesity, family history of diabetes mellitus, Down syndrome and CNS disease at diagnosis as risk factors for the development of hyperglycemia. Insulin is required in 39–75% of children with transient hyperglycemia (TH) and some have developed diabetic ketoacidosis and hyperosmotic non-ketotic coma.[8,9] Moreover, patients who develop hyperglycemia during induction chemotherapy may face increased risk of developing complicated infections as well as increased overall mortality and disease recurrence.[7]

Materials and Methods:

It was a prospective observational study in which consecutive purposive sampling was done. Primary purpose was to determine the frequency and identify the risk factors for hyperglycemia in children with acute lymphoblastic leukemia during induction chemotherapy. All newly diagnosed admitted children with ALL, between 1-18 years of age in department of Paediatric Hematology and Oncology, BSMMU during the study period from September 2015 to August 2016 were enrolled. Exclusion of patients were done according following criteria: age less than 1 year and 18 years or more, known case of diabetes mellitus and patients who were treated with glucocorticoid for other indications previously. Total 87 patients were enrolled in this study. Informed written consent from the parent or caregiver was obtained before enrollment. Data were collected using a preformed data collection sheet (questionnaire). Demographic data, medical data, clinical information were taken. The anthropometric measurements were taken for body weight, height and BMI which was taken by standard techniques. Then anthropometric indices were calculated using reference median as recommended by NCHS (WHO-2000) and classified according to standard deviation units termed as Z score. Body Surface Area (BSA) in square meter was determined by using nomogram and which used to calculate IV fluid rate. BMI was calculated by using formula weight/ height^2.

All the enrolled patients received hydration following induction chemotherapy according to UK-ALL 2003 protocol (modified), Regimen A or B guidelines.[15] Five percent dextrose with half strength normal saline or 5% dextrose with ¼ strength normal saline were the fluid of choice, allopurinol and aluminum hydroxide (without potassium) at 100–125 ml/m^2/hour for tumor lysis precautions. The criterion for insulin treatment was variable which generally included presentation of diabetes symptoms (e.g., polyuria, polydypsia) and a failure to respond to conventional measures (restriction of fluids with glucose).[8] Complete blood count, Random Blood Sugar (RBS) and corresponding urine sugar were estimated before starting induction chemotherapy along with other initial work up for a case of ALL. Hyperglycemia was defined as a plasma glucose concentration of ≥200 mg/dl (11.1 mmol/l) in two or more determinations during the first 35days of induction therapy. Blood glucose was measured by glucometer (Accu-chek, Roche, India). CBC, RBS/ 2 hr after glucose/ FBS and corresponding urine sugar was assessed again after 2nd, 4th, 6th and 9th dose of L-asparaginase and after completion of induction. HbA1c was measured in those patients who had hyperglycemia. Among total 87 patients 5 took discharge against medical advice before starting of the therapy. So, data were analyzed among 82 subjects. After collection and compilation data were analyzed by SPSS 17.0 version. Odds ratio of developing hyperglycemia was calculated for each variable. Chi-square analysis was used to determine the magnitude of difference in prevalence of hyperglycemia. Multivariate logistic regression analysis was performed to control for confounding factors.

Results:

After enrollment of total 87 patients data were analyzed among 82 subjects as 5 patients took

discharge before starting of the therapy. Among those 82 patients 74 were alive, 8 died. In this study, most of the patients were below 10 years (76.8%) and 67.1% were male. On BMI category, 3.75% were obese 6.25% were overweight and the remaining was in normal or underweight group. Mean RBS was 5.04 (±0.90) mmol/l.

Approximately 9.75% (8/82) of the ALL patients were found hyperglycemic but considering transient hyperglycemia (TH) two patients were deducted as because one patient developed diabetes mellitus who was on oral hypoglycemic agent and another patient required much higher time (456 hours) to resolve hyperglycemia. So frequency of Transient Hyperglycemia (TH) among study population was 7.3% (6/82).

Considering age as a risk factor, age ≥10 years having more hyperglycemic episode (36.8%) comparing age <10 years (1.6%). (p <0.001). Among female 18.5% had hyperglycemia while 5.5% in case of male, indicating female had a higher frequency of hyperglycemia than male. (P= 0.061). Patient having positive family history, 17.5% of them having hyperglycemic events compared only 2.4% of those having no such history. (p= 0.021). Having BMI ≥95th percentile for age, 100% of them had hyperglycemia and <95 percentile group 6.5% had hyperglycemia. OR cannot be calculated because a cell frequency is 0 and p value was<0.001. Again considering BMI e"85 percentile for age 75% of them had hyperglycemia and <85 percentile group 2.8% had hyperglycemia. (p <0.001). Fifty percent of patient having CNS disease at diagnosis had hyperglycemia, while 8.75% had hyperglycemia who had no CNS manifestation. (p= 0.052). Considering total count 10.7% of patient having <50,000/cmm had hyperglycemia, while 7.7% of patient having ≥50,000/ cmm had hyperglycemia. (P= 0.668). Considering number of drugs used during induction period as a risk factor, 17.5% of patient using 4 drugs had hyperglycemia while 2.4% who used 3 drugs. (p= 0.021). While multivariate analysis of the risk factors was done to see the development of hyperglycemia it was found BMI ≥95th percentile, in a multivariate analysis age ≥10 years was statistically significant (P= 0.001) but when BMI was ≥85th percentile none of the parameter statistically significant.

Table-I

Demographic characteristics of the study subjects (n=82)

Character	No. (%)
Age	
<10 Years	63(76.8%)
≥10 Years	19 (23.2%)
Gender	
Female	27 (32.9)
Male	55 (67.1%)
BMI category*	
Normal or underweight (< 85th percentile)	72 (90%)
Overweight (≥85th to 95th percentile)	5 (6.25%)
Obese (≥95th percentile for age)	3 (3.75%)

N.B: (*) age under 2 years was not included in BMI calculation. So, the number of patients was 80 when BMI was calculated.

Table-II

Clinical presentation of study subjects at diagnosis (n=82)

Presentation at diagnosis	No.	(%)
General condition		
Well	2	2.4
Sick	60	73.2
Toxic	20	24.4
Pallor		
Mild	42	51.2
Moderate	21	25.6
Severe	19	23.2
Lymphadenopathy	58	70.7
CNS involvement	02	2.4
Bleeding manifestation	42	51.2
Bone & joint pain	62	75.6
Hepatomegaly	82	100.0
Splenomegaly	70	85.4

Table-III

Laboratory findings of study subjects at diagnosis (n=82)

	Mean (±SD)	Min-Max
WBC (per cmm)	80557.93 (±144461.2)	740-663200
RBS (mmol/l)	5.04 (±0.90)	3.30 – 7.80
Serum LDH (U/L)	2421.41 (±2328.02)	384 - 10424

WBC (White Blood Cell), RBS (Random Blood Sugar), LDH (Lactate Dehydrogenase)

Table-IV

Hyperglycemia by risk factors among study subjects (n=82)

Characteristic	Total No. of cases	Number (%) with hyperglycemia	OR (95% CI)	P-value
Hyperglycemia	8			
Age				
< 10 years	63	1 (1.6)	36.167 (4.07 - 321.4)	**< 0.001**
≥10 years	19	7 (36.8)		
Gender				
Female	27	5 (18.5)	3.939 (0.865 - 17.93)	0.061
Male	55	3 (5.5)		
Positive Family History of Diabetes Mellitus	40	7 (17.5)	8.697 (1.018 - 74.27)	**0.021**
BMI (Percentile for age) *				
≥95th Percentile	3	3 (100.0)	**	**< 0.001**
<95th Percentile	77	5 (6.5)		
BMI (Percentile for age) *				
≥85th Percentile	8	6 (75.0)	105 (12.48 - 833.49)	**< 0.001**
<85th Percentile	72	2 (2.8)		
Presence of CNS disease at diagnosis	2	1 (50)	10.42(0.586 -185.45)	0.052
WBC count at diagnosis (/cmm)				
≥50,000	26	2 (7.7)	1.44 (0.270 - 7.67)	0.668
<50,000	56	6 (10.7)		
Number of drugs used during induction chemotherapy			8.697 (1.018 -74.27)	
3 drugs (Regimen A)	42	1 (2.4)		**0.021**
4 drugs (Regimen B)	40	7 (17.5)		

BMI (Body Mass Index), CNS (Central Nervous System), OR (Odds Ratio), CI (Confidence Interval)

(*) Age under 2 years was not included in BMI calculation. There were 2 patients below 2 years of age. So the number of patients was 80 while calculating BMI.

(**) odds ratio could not be calculated because a cell frequency was 0

Table-V

Multivariate analysis of the risk factors for the development of hyperglycemia (n=80)

Risk Factor	OR (95% CI)	P-value
A. Multivariate analysis with BMI divided at 95th percentile		
Gender	3.6 (0.567 – 23.4)	0.150
Age ≥10 years	20 (2.05 – 195.0)	**0.001**
Family history of DM	4.727 (0.503 – 44.396)	0.139
High WBC count at diagnosis (> 50,000 /cmm)	0.226 (0.02 – 2.62)	0.234
No. drug use during induction phase (4 drug)	4.727 (0.503 – 44.396)	0.139
B. Multivariate analysis with BMI divided at 85th percentile		
Gender	1.0 (0.041 – 24.55)	0.786
Age ≥10 years	5.0 (0.150 – 166.59)	0.346
Family history of DM	5.0 (0.150 – 166.59)	0.346
High WBC count at diagnosis (> 50,000 /cmm)	2.0 (0.078 – 51.59)	0.673
No. drug use during induction phase (4 drug)	0.121 (0.014 – 1.034)	0.537

BMI (Body Mass Index), OR (Odds ratio), CI (Confidence interval)

Table VI

Hyperglycemic patient's characteristics, insulin requirement, time required to normalization of blood glucose level, RBS and HbA1c level when hyperglycemia occurred (n=8)

Sl No	ID No	Age ≥10 years or <10 years	Sex M/F	When Hyperglycemia developed (IR day)	Insulin required (Yes/ No)	Time required to normalization of blood glucose level (Hours)	RBS level when hyperglycemia occurred		HbA1c level when hyperglycemia occurred	
							mmol/l	Mean (±SD)	%	Mean (±SD)
01	001	≥10 years	F	Day 7	Yes	456	27.3		6.3	
02	020	<10 years	M	Day 10	Yes	07	14.4		4.6	
03	027	≥10 years	F	Day 12	No	13	16.8	20.51	5.5	5.46
04	031	≥10 years	F	Day 09	No	11	15.8	(± 7.71)	5.2	(±0.85)
05	045	≥10 years	M	Day 20	No	*	12.0		6.9	
06	047	≥10 years	M	Day 8	Yes	01	30.4		**	
07	063	≥10 years	F	Day 18	Yes	17	31		4.8	
08	082	≥10 years	F	Day 11	No	14	16.4		4.9	

M= Male, F=Female, SD=Standard Deviation, RBS= Random Blood Sugar, HbA1c= Glycated Hemoglobin

* Blood glucose level was persistently high and now on oral hypoglycemic.

**Patient had died before sending blood sample for HbA1c (missing data)

Discussion

Frequency of hyperglycemia was found 9.75% in this study which was similar to previous study of Castro AMS et al.[4] Baillargeon et al. and Pui et al. reported the rates in the range of 10 to 11%.[8,10] The study by Pui et al. was performed in the early 1980s, when there may have been a different prevalence of the risk factors that have been associated with this condition including obesity and ethnic background.[10] Sonabend et al. reported an extremely high prevalence of hyperglycemia (34%) during remission induction.[18] This may be attributed to the fact that blood glucose levels were measured postprandially and a single measurement of glucose greater than 200 mg/dL was sufficient to be included in the study group.

Children in the older (≥10 years) age group exhibited such a dramatic increase in the incidence of hyperglycemia. Pui et al. and Koltin et al. reported similar findings, indicating that children aged 10 years and older had an elevated risk of developing therapy-induced hyperglycemia compared to younger aged patients.[10,12] It is probable that this age effect simply reflects the elevated insulin resistance associated with gonadal steroids during puberty.

Considering gender as a risk factor hyperglycemia was occurred more frequently in female than male but it was not statistically significant which were same as previous reports.[9,12]

The incidence of hyperglycemia in this study (17.5%) was significantly higher among patients with a family history of diabetes mellitus. Pui et al. found its 20%, which would imply that a genetic factor likewise contributes to the development of hyperglycemia in patients treated with L-asparaginase and dexamethasone.[10] This association must be considered tentative until verified in a careful prospective study.

BMI was considered the best single weight–height measure in both children and adults with respect to independence of height, correlation with body fat, and prediction of mortality. This definition was based on the recommendations of an expert panel on childhood obesity and was in accordance with previous studies.[19-21] Because of the CDC recommendation to use BMI values only after the age of two years, subjects under the age of two was not included in the BMI analysis. In this study obese children (≥95th percentile) or the children who were overweight (≥85th percentile) exhibited an increased risk for development of hyperglycemia. In both cases the p-value were significant (<0.001). Sonabend et al., Baillargeon et al., and Lowas et al. all described the overweight state (BMI > 85th percentile) as a risk factor.[1,8,9] Koltin et al. found BMI percentile among those with hyperglycemia did not differ from those without hyperglycemia.[12]

Ortega et al. suggested that high leukocyte count was a predisposing factor for hyperglycemia.[22] By contrast, even after adjustment for age, initial leukocyte count in this study had no demonstrable association with the frequency of hyperglycemia which was found in another study.[12] In this study, using 4 drugs/ Regimen B during induction of remission phase associated with an increased risk for the development of hyperglycemia which was similar to that found in previous studies.[12]

Conclusion

Risk factors for hyperglycemia in children with ALL include age ≥10 years, positive family history of diabetes mellitus among first and second degree relatives, obese or overweight child, using four drugs (protocol B) during induction remission chemotherapy.

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