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Hyperglicemia in Childhood Acute Lymphoblastic Leukemia During Induction Chemotherapy

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Abstract

Background: Hyperglycemia is a recognized side effect of the corticosteroids and asparaginase given during induction chemotherapy for pediatric acute lymphoblastic leukemia (ALL). The ALL is the malignant tumor with the highest incidence in the childhood. The aim of this study is to investigate the impact of hyperglycemia during induction chemoteraphy in childhood ALL.

Methods: This prospective study was done in Dr. Soetomo hospital from January to April 2018. The subject was newly diagnosed as ALL under the age of 18 years, treated with Indonesian childhood ALL 2013 protocol (Standard Risk (SR) group and High Risk (HR) group). Hyperglycemia was defined as at least two separate random plasma glucose levels > 200 mg/dL, which was evaluated before and during induction chemotherapy. Statistical analysis using Paired T-test for parametric and Wilcoxon Test for nonparametric.

Results: Thirty-three children were enrolled, 18/33 boys with mean age 5.8 (SD 3.78) years, compromised as ALL-L1 30/33. They were treated with ALL-HR 19/33 and ALL-SR 14/33. In overall groups, the mean random blood glucose level significantly increased from 108 (SD 21.3) mg/dL to 147 (SD 48.1) mg/dL, (mean difference 38.67 mg/dL; 95% CI 18.08 to 59.26 mg/dL, P=0.008). In SR group, there was a significant increased of mean random blood glucose level from 102 (SD 13.5) mg/dL to 133 (SD 37.3) mg/dL, (mean difference 31.8 mg/dL; 95% CI 8.78 to 54.8 mg/dL; P=0.01). In HR group, the mean random blood glucose level increased from 113 (SD 51.9) mg/dL to 165 (SD 25.4) mg/dL, (mean difference 51.9 mg/dL; 95% CI 18.6 to 85.2 mg/dL, P=0.004).

Conclusion: Blood glucose level is significantly increase during induction chemotherapy in both SR and HR Indonesian childhood ALL 2013 protocol.

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Keyword: *Hyperglycemia, acute lymphoblastic leukemia, childhood.*

Background

Hyperglycemia is a common side effect of acute lymphoblastic leukemia (ALL) therapy. It 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 phase, with resolution after the steroids and asparaginase have been discontinued or reduced in dose. [1-4] The potential causes may include beta cell dysfunction caused by chemotherapeutic drugs such as L-asparaginase, increased insulin resistance and hepatic gluconeogenesis induced by corticosteroids, or synergistic effects of these medications, given that these pharmacological agents are usually combined during initial induction therapy. [1,4] The spectrum of hyperglycemia can range widely from transient isolated episodes to severe life-threatening complications such as diabetic ketoacidosis or nonketotic hyperglycemic hyperosmolar syndrome.[5-7] Transient hyperglycemia developed during this period largely resolves as the chemotherapy is discontinued.[3] However, affected children may need longer hospitalization and delay in chemotherapy; they may experience increased infective incidence and may even have poorer survival outcomes.[8,9]

Previous studies have documented hyperglycemia induced by chemotherapy occur in 0.2- 16%. Few published data have referred to the epidemiology of treatment-related hyperglycemia in Indonesian childhood ALL. The purpose of the current study is to evaluate the incidence of hyperglycemia during the induction chemotherapy for childhood ALL in Dr. Soetomo Hospital.

Methods

This is a prospective study involving of consecutive patients, age younger than 18 years, in whom ALL was diagnosed and who were admitted to Dr. Soetomo hospital, Surabaya between January and April 2018.

We excluded patients with previously diagnosed diabetes mellitus (DM) or who were treated with glucocorticoids were also excluded. Medical records were reviewed to obtain relevant clinical data, including demographic information, such as age at diagnosis, sex, weight, height, and clinical parameters, such as initial white blood cell count (WBC), initial C-reactive protein (CRP) level, initial plasma glucose level, immunotyping of leukemic cells, and risk classification. Hyperglycemia was defined as at least two separate random plasma glucose levels ³200 mg/dL according to the published guidelines for childhood diabetes.[10] Plasma glucose level was evaluated before and during induction chemotherapy. BMI was calculated by dividing weight in kilograms by height in square meters. Using reference standards from the Centers for Disease Control and Prevention (CDC), each subject's body mass index (BMI), BMI percentile for age, and BMI z-score for age were calculated. Per current CDC guidelines, subjects with BMI greater than or equal to the 95th percentile for age and gender were defined as overweight and those with BMI greater than or equal to the 85th percentile for age and gender were defined as at risk for overweight.[11] All patients were treated according to the Indonesian childhood ALL 2013 protocol. The 1st day of treatment was designated when the use of steroids was started. The entire procedure was approved by the Ethic Committee Dr. Soetomo Hospital, Surabaya.

All of the data collected were entered into an SPSS database (SPSS version 21.0.0.0). Descriptive statistics about the subject population were calculated, including data such as sex, age, and BMI at diagnosis. Presence of hyperglicemia was defined as above. Proportions of subjects with hyperglicemia overall and within each population category group (High risk and standard risk group) were calculated. For this analysis, subjects were divided by high risk and standard risk group as defined above. Chi-square analysis was used to determine the magnitude of difference in prevalence of hyperglycemia between groups. Statistical analysis using Paired T-test for parametric and Wilcoxon Test for non parametric. P values < 0.05 were regarded as significant.

Results

Thirty-three children were enrolled during our study period. All study subjects were newly diagnosed with ALL and received induction chemotherapy between January and April 2018. There were 18/33 boys and 15/33 were girls, the mean age of the patients when initially diagnosed was 5.8 (SD 3.78) years old. The patients compromised as ALL-L1 30/33 patients. They were treated with ALL-HR 19/33 patients and ALL-SR 14/33 patients. Baseline characteristics at the time of

testing are shown in Table 1.

In overall groups, 6/33 patients experienced hyperglycemia during induction chemotherapy, five of them treated with ALL-HR regimen and one treated with ALL-SR regimen. There is no significant incidence of hyperglycemia between ALL-HR and ALL-SR with p value 0.117 (Table 2). In overall groups, the mean random blood glucose level significantly increased from 108 (SD 21.3) mg/dL to 147 (SD 48.1) mg/dL, (mean difference 38.67 mg/dL; 95% CI 18.08 to 59.26 mg/dL, P=0.008).

Table 1. The baseline characteristics of the patients

Characteristics	Number (%)
Sex	
Male	18 (54.5)
Female	15 (45.5)
Age	
<10 y	27(81.8)
□10 y	6 (18.2)
Nutritional status	
Undernourished	16 (48.5)
Well-nourished	16 (48.5)
Overweight	1 (3)
Obese	0
CRP	
< 20mg/dL	27 (81.8)
□20 mg/dL	6 (18.2)
Risk group	
Standard risk	14 (42.4)
High risk	19 (57.6)

In overall groups, the mean random blood glucose level significantly increased from 108 (SD 21.3) mg/dL to 147 (SD 48.1) mg/dL, (mean difference 38.67 mg/dL; 95% CI 18.08 to 59.26 mg/dL, P=0.008). In SR group, there was a significant increased of mean random blood glucose level from 102 (SD 13.5) mg/dL to 133 (SD 37.3) mg/dL, (mean difference 31.8 mg/dL; 95% CI 8.78 to 54.8 mg/dL; P=0.01).

Table 2. Hyperglycemia in ALL HR and ALL SR

Diagnosis	Hyperglicemia		Total	P value
	Yes	No		
ALL HR	5	13	18	
ALL SR	1	14	15	
Total	6	27	33	0.117

In HR group, the mean random blood glucose level increased from 113 (SD 51.9) mg/dL to 165 (SD 25.4) mg/dL, (mean difference 51.9 mg/dL; 95% CI 18.6 to 85.2 mg/dL, P=0.004), the increased blood glucose during induction chemotherapy are demonstrated in Table 3.

Table 3. Increased blood glucose during induction chemotherapy

Groups	Before chemotherapy	During chemotherapy	Mean (95 % CI)	P value
ALL HR	113 (SD 51.9)	165 (SD 25.4)	51.9 (18.6- 85.2)	0.004
ALL SR	102 (SD 13.5)	133 (SD 37.3)	31.8 (8.78 – 54.8)	0.01
Overall	108 (SD 21.3)	147 (SD 48.1)	38.67(18.08- 59.26)	0.008

Discussion

In this study, 33 children with newly diagnosis of acute lymphoblastic leukemia that treated in Dr Soetomo hospital and were in induction chemotherapy of their treatment, evaluated for hyperglycemia. These Children followed for six weeks and were assessed for growth parameters, and blood sugar. Hyperglycemia defined when at least two random glucose level >200 mg/dl. According to these criteria, there were six cases with hyperglycemia (18% of the subjects). In a study by Banihashem et al, 32 patients with a diagnosis of acute leukemia, and 17.2% of patients had hyperglycemia.[12]

In this study, there was no significant difference between incidence of hyperglycemia and type of treatment according to Indonesia childhood ALL protocol 2013 (chi-square p=0.117). This result similar with Banihashem study, which is there was no significant difference between incidence of hyperglycemia and different protocol of chemotherapy that used for treatment of children (chi-square p=0.983).[12] The similar study was a study by Baillargeon et al. that evaluated transient hyperglycemia in Hispanic children with Acute Lymphoblastic Leukemia, and 11.0% of the study cohort developed hyperglycemia during induction chemotherapy.[4]

In this study, the blood glucose level is significantly increase in all groups during induction chemotherapy, overall with p value 0.008, p value 0.004 and 0.01 in HR groups and SR groups, respectively.

At a literatue by Lowas et al. Prevalence of transient hyperglycemia during induction chemotherapy for pediatric acute lymphoblastic leukemia was assessed. Transient hyperglycemia (TH) is a recognized side effect of the corticosteroids and asparaginase given during induction chemotherapy for pediatric acute lymphoblastic leukemia (ALL). This study examined the prevalence of TH in a cohort of pediatric ALL patients and the impact on TH of type of steroid or asparaginase.[13]

Hyperglycemia and diabetes induced by chemotherapy occur in the range of 0,2% to 16% (see table 4). Pui et al reported hyperglycemia in 9,7% of the pediatric ALL patients in the induction period of chemotherapy, after receiving prednisone and L-asparaginase.[3] Weiser et al documented an incidence of hyperglycemia in 37% of patients during induction chemotherapy.[14] According to Pastore et al 50% of ALL children may develop hyperglycemia, whereas Banihashem et al reported that 27,5% of the pediatric patients showed either diabetes mellitus or hyperglycemia.[12]

There is a complex pathophysiology mechanism that explains the development of hyperglycemia in the pediatric population receiving induction chemotherapy. DeFronzo et al have described a series of events that lead to genesis of diabetes as follow:1) some patients showed a predisposition to enhance insulin resistance and propensity for ß-cells failure, 2) specific risk factors such as preexisting obesity reinforce these defects, 3) diabetes mellitus comes up, when a concomitant insulin secretory defect is present, regardless of the etiology.[15]

During the standard treatment of ALL, children receive 3 drugs in the first month of the therapy. These include L-asparaginase, Vincristine and steroids as prednisolone. Children in high risk group of ALL receive a fourth chemotherapy drug, mostly daunorubicin. During the standard treatment of ALL, children receive 3 drugs in the first month of the therapy. Additionally, intrathecal chemotherapy using commonly methotrexate is performed. L-asparaginase inhibits insulin protein synthesis.[16] L-asparaginase may directly reduce the glucose-stimulated release of insulin from ß- cells and indirectly reduce insulin production by causing pancreatitis. Furthermore, it is known, that corticosteroids induce insulin resistance. These effects may lead to the development of diabetes mellitus in children receiving chemotherapy, and more often in those with additional risk factors.[16,17]

Hyperglycemia occurs commonly in the pediatric population receiving induction chemotherapy, but a combination of glucocorticoids and L-asparaginase may cause diabetes mellitus. Physicians should be aware of these risk factors and perform an early and careful screening for hyperglycemia (fasting glucose levels) during the treatment of the patients with ALL. [18]

Furthermore, application of the right treatment for hyperglycemia, such as insulin, permits an early clinical and biochemical normalization and enforces thereby the continuation of the chemotherapy. The use of insulin may reduce the period of hyperglycemia and therefore the possible future metabolic side effects.

Conclusion

The incidence of hyperglycemia is not significant in this study, but blood glucose level is significantly increase during induction chemotherapy in both SR and HR Indonesian childhood ALL 2013 protocol. Therefore, we recommend clinicians should be aware of the risk of hyperglycemia in childhood ALL during the induction chemotherapy. Future investigations of pediatric cohorts are needed to evaluate the influence and outcome of transient hyperglycemia as well as diabetes mellitus for long-term survival and metabolic syndrome.

Conflict of Interest : None declared

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Ethical Clearance: Taken from Ethic Committee Dr. Soetomo Hospital, Surabaya.

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