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Original Article

Blood glucose level during induction phase chemotherapy in childhood acute lymphoblastic leukemia

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Abstract

Background Steroids and L-asparaginase (L-Asp) are agents used in induction phase chemotherapy for childhood acute lymphoblastic leukemia (ALL). Both agents are often reported to have the side effect of hyperglycemia, and native L-Asp is also reported to cause hypoglycemia. In ALL patients, hyperglycemic events during chemotherapy can cause lower 5-year overall and relapse-free survival.

Objective To investigate the incidence of abnormal blood glucose level (BG) as the side effect of prednisone and L-Asp during induction phase chemotherapy, its predisposing factors, and its effect on remission status.

Methods This cohort prospective study was conducted in 36 children aged 1-18 years who were newly diagnosed with childhood ALL at Dr. Moewardi Hospital, Surakarta, Central Java. Subjects' nutritional status consist of wellnourished and undernourishment. Subjects underwent BG monitoring. At the end of induction phase chemotherapy, subjects underwent bone marrow puncture (BMP) evaluation to assess their response to chemotherapy and the effect of abnormal BG on remission status.

Results Hypoglycemia, a combination of hypoglycemia and hyperglycemia, hyperglycemia, as well as euglycemia, were experienced by 9, 7, 6, and 14 subjects, respectively. Nutritional status was found to be a significant risk factor for abnormal BG. There was no significant difference in remission status at the end of induction phase chemotherapy between the euglycemic group and abnormal BG groups (P=0.533).

Conclusion Abnormal BG during induction phase chemotherapy did not affect remission status at the end of induction phase. Undernourishment is also found to be a predisposing factor in abnormal BG. **[Paediatr Indones. 2020;60:192-7; DOI: 10.14238/pi60.4.2020.192-7]**.

Keywords: *blood glucose; hyperglycemia; hypoglycemia; L-asparaginase; steroids; leukemia*

Acute lymphoblastic leukemia (ALL) is the most common pediatric malignancy.[1,2] Chemotherapy is still the main therapy for childhood ALL. Steroids and L-Asp are agents used in inductive phase chemotherapy known to have hyperglycemia as a side effect.[3-5] A previous study reported that hyperglycemia during inductive phase chemotherapy was associated with lower 5-year overall and relapse-free survival.[6] Native L-Asp, produces more incidences of hypoglycemia than hyperglycemia during chemotherapy for childhood ALL.[7] To our knowledge, there have been no studies on the impact of hypoglycemia during chemotherapy on survival rate. As such, we aimed to investigate the incidence of abnormal blood glucose level (BG) as the side effect of prednisone and L-Asp used in inductive phase chemotherapy, predisposing factors of abnormal BG, and the effect of abnormal BG on remission status.

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Methods

This prospective cohort study was conducted to analyze the effect of abnormal BG caused by prednisone and L-Asp treatment on remission status in subjects treated in the Pediatric Hemato-Oncology Ward, Dr. Moewardi General Hospital, Surakarta, Central Java, Indonesia. The study was performed between June 2018 and June 2019. Subjects were pediatric patients newly diagnosed with ALL, aged between 1 and 18 years, who underwent chemotherapy following the Indonesia ALL 2018 high risk or standard risk protocol.8 All the participants' parents or caregivers provided written informed consent prior to this study. Patients with abnormal BG before chemotherapy, HbA1C ≥ 6.5%, or incomplete induction phase were excluded from the study. The ALL diagnoses were established with bone marrow puncture (BMP) examinations. Patients were followed from the time of established diagnosis until BMP evaluations at the end of induction phase chemotherapy, a total period of 8 weeks. For baseline, HbA1C measurements as well as fasting and two-hour postprandial BG examinations were done before the chemotherapy started. In addition, fasting and two-hour postprandial BG evaluations were done at the end of each week during induction phase chemotherapy. In particular weeks when L-Asp was added for chemotherapy, BG examinations were done after the second dose. The baseline characteristics of subjects were sex, age, risk stratifications, and nutritional status. At the end of inductive phase, all subjects were evaluated with BMP examinations. Complete remission was achieved when blast cells were <5%, incomplete remission was defined as blast cells 5% - 20%, and no remission was defined as blast cells >20% of the 200 nucleated cells in bone marrow. Incomplete remission was categorized as no remission.

Blood glucose of <65 mg/dL and 65-199 mg/dL were defined as hypoglycemia and euglycemia, respectively, while hyperglycemia was described as BG ≥126 mg/dL for fasting or ≥200 mg/dL for two-hour postprandial exams.9,10 The subjects were divided in two groups, euglycemia (normal BG during induction phase chemotherapy) and abnormal. The abnormal group was sub-divided into three subgroups: hypoglycemia (≥ 1 episode of hypoglycemia), combination hypoglycemia and hyperglycemia (≥ 1 episode of hypoglycemia and ≥ 1 episode of hyperglycemia), or hyperglycemia (≥ 1 episode of hyperglycemia) during induction phase chemotherapy.

We analyzed for possible associations between abnormal BG and sex, age, risk stratification, and nutritional status. Age was divided into <10 years and ≥10 years. Risk stratifications were classified into standard risk and high risk, based on the Indonesia ALL 2018 protocol. Nutritional status was assessed with weight per height measurements and categorized based on Waterlow 1972.11 Data were analyzed with SPSS version 21.0. Bivariate analysis was done by Chi-square test and was followed by multivariate logistic regression analysis. This study was approved by the Health Research Ethics Committee of Universitas Sebelas Maret Medical School/Dr. Moewardi Hospital Surakarta.

Results

Forty-five children were diagnosed with ALL during study period, but two were excluded due to hyperglycemia before chemotherapy. The remaining 43 patients were included, but 7 died before completing the induction phase, hence, 36 subjects completed the study. The subjects' baseline characteristics are presented in **Table 1**. Half of the subjects were female. Twenty-four subjects were under 10 years of age, 25 subjects were in the high risk stratification category, and 20 subjects were well-nourished (**Table 1**).

Blood glucose exams during induction phase demonstrated hyperglycemia in 6 subjects, hypoglycemia in 9 subjects, hypoglycemia and hyperglycemia in

Table 1. Baseline characteristics of subjects

Characteristics	(N=36)
Gender, n	
Male	18
Female	18
Age, n (%)	
<10 years	24
≥10 years	12
Risk stratification, n	
High risk	25
Standard risk	11
Nutritional status, n	
Well-nourished	20
Undernourished	16

7 subjects, and euglycemia in 14 subjects. The onset of abnormal BG is shown in **Table 2**. Seven subjects did not have remission after completing the induction phase (**Table 3**).

Five of the 7 subjects who did not achieve remission were from the abnormal BG group. However, there was no significant difference between remission status in the euglycemia and abnormal BG group (P=0.533) (**Table 4**). Bivariate analysis of potential predisposing factors (sex, age, risk stratification, and nutritional status) to BG during induction phase revealed that only nutritional status was significantly correlated with abnormal BG **(Table 5)**.

Multivariate logistic regression analysis was performed to to further study the correlation between abnormal BG and age and nutritional status, the two variables with P<0.25 in bivariate analysis. Age ≥ 10 years had no significant correlation with abnormal BG (P=0.396), however, undernourished nutritional status had a significant correlation with abnormal BG (P=0.005) (**Table 6**).

Discussion

The ALL survival rate has been improved to 90%.[12] Chemotherapy for ALL including induction, consolidation, and maintenance phases lasts for 2-3 years.[13] Two agents used in the induction phase, steroids and L-Asp, have been documented to cause hyperglycemia. The predominant mechanism of steroid-increased BG level is by induction of insulin resistance.[3,4] The risk of hyperglycemia increases when L-Asp is co-administered.[14] A study reported that the incidence of hyperglycemia as a side effect of steroid and L-Asp combination was 5.2%, from three centers in Indonesia.[15] We found that 6 subjects (16.6%) experienced hyperglycemia when they received prednisone as well as L-Asp simultaneously during the induction phase, with fasting BG ranging from 130 mg/dL to 311 mg/dL , and 329 mg/dL in one episode of two-hour postprandial BG. Native L-Asp, on the contrary, was reported to result in more hypoglycemia than hyperglycemia during

Table 2. Onset of abnormal BG during induction phase chemotherapy

Abnormal BG	Subjects	Weeks								BG level (range)
		0	1	2	3	4	5	6	7	
Hyperglycemia		2	3	1	-	-	-	-	-	Fasting: 130-311 mg/dL 2PP: 329 mg/dL
Hypoglycemia		2	-	7	-	-	-	-	-	Fasting: 40-64 mg/dL 2PP: 58 mg/dL
Hypoglycemia and hyperglycemia (subjects experiencing hypoglycemia then followed by hyperglycemia)	Subject I	hypo					hyper			Hypoglycemia: Fasting: 56-64 mg/dL 2PP: N/A Hyperglycemia: Fasting: 267 mg/dL 2PP: 211-388 mg/dL
	Subject II			hypo	hyper					
	Subject III		hypo hyper							
Hyperglycemia and hypoglycemia (subjects experiencing hyperglycemia then followed by hypoglycemia)	Subject I		hyper		hypo					Hyperglycemia: Fasting: 131-205 mg/dL 2PP: 211 mg/dL Hypoglycemia: Fasting: 53-63 mg/dL 2PP: N/A
	Subject II			hyper		hypo				
	Subject III				hyper	hypo				
	Subject IV	hyper			hypo					

Hyper=hyperglycemia; hypo=hypoglycemia; 2PP: 2 hours post prandial

Table 3. Blood glucose level during inductive phase chemotherapy and BMP after chemotherapy

Variables	(N=36)
Blood glucose levels, n	
Hypoglycemia	9
Hypoglycemia-hyperglycemia	7
Hyperglycemia	6
Euglycemia	14
Bone marrow puncture, n	
Complete remission	29
No remission	7

Table 4. The effect of abnormal BG on remission status

	No remission	Complete remission	OR (95%CI)	P value
Abnormal	5	17	1.765 (0.292 to 10.661)	0.533
Euglycemia	2	12		

Chi-square test

Table 5. Bivariate analysis of BG and potential predisposing factors

Variables	Euglycemia (n=14)	Abnormal (n=22)	OR (95%CI)	P value
Gender, n			1.600 (0.414 to 6.177)	0.494
Male	8	10		
Female	6	12		
Age, n			0.294 (0.069 to 1.249)	0.091
<10 years	7	17		
≥10 years	7	5		
Risk stratification, n			1.167 (0.269 to 5.054)	0.837
High	10	15		
Standard	4	7		
Nutritional status, n			27.857 (3.016 to 257.267)	0.000
Well-nourished	13	7		
Undernourished	1	15		

Table 6. Multivariate logistic regression analysis

	OR (95%CI)	P value
Age (>10 years)	0.468 (0.081 to 2.707)	0.396
Nutritional status (undernourished)	24.353 (2.590 to 228.958)	0.005

chemotherapy in childhood ALL.[7] Seven of 9 subjects in our hypoglycemia group suffered from hypoglycemia after the second dose administration of L-Asp in the second week, with fasting BG ranging from 40 mg/dL to 64 mg/dL, and 58 mg/dL in one episode of two-hour postprandial BG. L-Asp-induced hypoglycemia occurs through hyperinsulinism.[16,17] However, we did not examine subjects' insulin level. Seven subjects had hypoglycemia as well as hyperglycemia, with 3 subjects experiencing hypoglycemia first, followed by hyperglycemia, with fasting BG ranging from 56 mg/dL to 64 mg/dL; none of them had two-hour postprandial hypoglycemia, whereas BG in the hyperglycemia episode ranged from 211 mg/dL to 388 mg/dL two-hour postprandial, and 267 mg/dL in one episode of fasting hyperglycemia. The other 4 subjects had hyperglycemia then hypoglycemia, with fasting BG ranging from 131 mg/dL to 205 mg/dL, and 211 mg/dL in one episode of two-hour postprandial BG. While BG in the episodes of fasting hypoglycemia ranged from 53 mg/dL to 63 mg/dL, and no episode of hypoglycemia in two-hour postprandial BG. Fourteen others had normal BG throughout induction phase.

Bivariate analysis revealed that age 10 years and over as well as undernourished nutritional status were significantly correlated with abnormal BG. This finding was in line with a study which noted that the most important predictor of hyperglycemia in pediatric ALL during chemotherapy was age older than 10 years.[18] However, upon further multivariate regression analysis in our study, age >10 years had no significant correlation with abnormal BG. Nevertheless, undernourished nutritional status was significantly correlated with abnormal BG in our multivariate analysis. A previous study discovered that malnourished children experienced insulin resistance affecting BG.[19]

A study reported that ALL subjects who experienced hyperglycemia during induction phase chemotherapy had lower 5-year overall and relapse-free survival than those with euglycemia.[6] However, to our knowledge there have been no studies about the effect of hypoglycemia on survival rate. In our study, all subjects were followed up until the BMP evaluation was performed in the end of induction phase, revealing that 7 subjects (19.4%) did not achieve remission, 5 of whom were from abnormal BG group.

The study limitations were not measuring subjects' total caloric intake per day and lack of data about family history of diabetes mellitus. Since our study only covered the induction phase of 8 weeks, we cannot describe the final outcomes of our subjects. In conclusion, abnormal BG in children with ALL undergoing induction phase chemotherapy has no significant association with remission at the end of induction phase, and undernourishment is correlated with abnormal BG in childhood ALL patients.

Conflict of interest

None declared.

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