Original Article 10.30477/CJM.2023.363122.1050

The effect of hyperglycemia during induction chemotherapy on the prognosis of pediatric acute lymphoblastic leukemia (ALL)

Aziz Eghbali[1], Roghayeh Rahimi Afzal[2], Aygin Eghbali[3], Ali Karbalaie[4,*], Behnaz Shabani Fouladi[4], Seyed Amir Sanatkar[5]

1. Aliasghar Clinical Research Development Center, Iran University of Medical Sciences, Tehran, Iran.
2. Department of Pediatrics, Arak University of Medical Sciences, Arak, Iran.
3. School of Medicine, Iran University of Medical Sciences, Tehran, Iran.
4. Students Research Committee, Arak University of Medical Sciences, Arak, Iran.
5. Department of Surgery, Arak University of Medical Sciences, Arak, Iran.

ABSTRACT

Background: Hyperglycemia is a common complication during treatment for acute lymphoblastic leukemia (ALL) and can be associated with multiple adverse outcomes. In this study, we investigated the effect of hyperglycemia during induction chemotherapy on response to treatment in pediatric ALL patients. **Material and methods:** We designed a cross-sectional study on 192 patients with acute lymphoblastic leukemia and divided them into the case (glucose value of ≥ 200 mg/dl) and control (no hyperglycemia) groups. After reviewing their hospital records, the two groups were compared in terms of length of hospital stay, nosocomial infection, delay in chemotherapy and remission, and survival rate, and the obtained data were analyzed using SPSS 21 software. **Results:** Of the 192 patients, 44 (22.91%) met previously defined criteria of hyperglycemia. The mean (±SEM) length of hospital stay in the case and control groups was 30.23 (±0.71) and 27.49 (±0.42) days, respectively (P = 0.002). In the case group, 23 patients (52.28%), and in the control group, 47 patients (31.75%) had delayed chemotherapy (P = 0.01). In the case group, 23 people (52.27%), and in the control group, 48 people (32.43%) developed nosocomial infections (P = 0.02). Everyone in the case group had a remission before a month; in the control also, only 2 (1.3%) didn't experience remission in a month. The rate of one-year survival in the case and control groups were 88.64% and 84.09%, and three-year survival was 86.48% and 83.1%, respectively. **Conclusion:** Hyperglycemia in pediatrics with ALL is associated with increased length of hospital stay, delayed chemotherapy, and nosocomial infection; however, there was no significant difference between the two groups in terms of remission and survival.

Keywords: Pediatric, Acute Lymphoblastic Leukemia, Hyperglycemia

Receive Date: 21 September 2023
Revise Date: 4 June 2023
Accept Date: 5 June 2023
Published Date: 24 September 2023
Editor: AR. Rafiei Javazm (Conflict of interest: None)
Reviewers: H. Baghsheikhi (Conflict of Interests: None), A. Mehdipour Arbastan (Conflict of Interests: None), HR. Mohammadi (Conflict of Interests: None), M. Sadri (Conflict of interest: None), SN. Salehi (Conflict of Interests: None)

*Correspondence to: Ali Karbalaie, Students Research Committee, Cancer Research Center, Arak University of Medical Sciences, Arak, Iran. Email: ali.karbalaie65110@gmail.com.
ORCID ID: **0000-0002-7564-7525**

Cite as : Aziz Eghbali, Roghayeh Rahimi Afzal, Aygin Eghbali, Ali Karbalaie, Behnaz Shabani Fouladi, Seyed Amir Sanatkar. The effect of hyperglycemia during induction chemotherapy on the prognosis of pediatric acute lymphoblastic leukemia (ALL). Canon Journal of Medicine. 2023 June; 4(2), 50-54.

INTRODUCTION

Acute leukemia is the most common type of cancer in children and accounts for 30% of all childhood malignancies (1). The prevalence of acute leukemia is 3 to 4 per 100 thousand children under 15 years of age, and the highest age range is 2 to 15 years old. Seventy-five percent of acute leukemia cases are acute lymphoblastic leukemia (2). With a 5-year survival rate of 40% for people aged 20 and older, and 89% for people aged under 20, Acute leukemia has a rapid clinical course and can lead to death within a few months without effective treatment (2). There is no known cause for leukemia, but genetic and environmental factors play an important role in the pathogenesis of this disease.

The primary treatment for ALL involves induction of remission, and the most commonly used drugs at this stage are vincristine, corticosteroids, and L-asparaginase (3). Asparaginase is a bacterial enzyme and a valuable chemotherapy drug used to treat and improve long-term survival in ALL patients (4).

Hyperglycemia was defined as more than one glucose value of ≥ 200 mg/dl during remission induction therapy (5). Hyperglycemia during chemotherapy in patients with ALL is believed to be due to the effect of asparaginase and glucocorticoids (5-8). Glucocorticoids lead to insulin resistance, while asparaginase inhibits insulin release from pancreatic beta cells and indirectly reduces insulin levels by causing pancreatitis (9). Most patients with hyperglyce-

mia improve with the discontinuation of glucocorticoid and asparaginase and do not show any long-term effects of hyperglycemia (4, 7, 9). However, careful evaluation and early treatment of these patients are essential in preventing ketoacidosis and non-ketotic hyperosmolar coma (9, 10).

Due to the relatively high prevalence of hyperglycemia in patients with acute lymphoblastic leukemia under induction therapy (10-50%) on one hand (11); and the fact that hyperglycemia may increase susceptibility to infection, prolong hospital stay, delay chemotherapy, remission, affect survival, and disrupt the patients' treatment protocol, on the other hand (12-14), we investigated the effect of hyperglycemia during induction chemotherapy on the prognosis of pediatric patients with acute lymphoblastic leukemia.

MATERIAL AND METHODS

STUDY DESIGN

We designed a cross-sectional study on 192 patients with acute lymphoblastic leukemia referred to AmirKabir Hospital, located in Arak, Iran, from 2009 to 2017. We matched the samples as possible in terms of age, sex, weight, and type of disease. Patients with ALL referred to AmirKabir Hospital were enrolled in the study after obtaining informed consent from the parent or guardian and age-appropriate permission from the patient. Then we defined the exclusion and inclusion criteria. The inclusion criteria were: patients with leukemia in the maintenance phase referred to AmirKabir Hospital, while the Exclusion criteria were: lack of cooperation to continue the study, documented previous history of diabetes mellitus, acanthosis nigricans, preexisting impaired glucose tolerance, Immunodeficiencies, HIV, liver diseases such as HBV or HCV, and patients who were already taking corticosteroids for the 6 months before their hospital stay.

DATA COLLECTION AND MEASUREMENTS

In this study, the hospital records of all patients with ALL were reviewed to obtain demographic information; treatment protocol; pre-existing diagnosis; leukemia risk category; dates of Complete remission, relapse; hospitalizations, and infections.

The strategy of risk stratification was established based on the National Cancer Institute (NCI)/Rome criteria; Standard-risk ALL patients must have both of the following criteria: The WBC count < 50,000 cells/mm3 (50.0 x 109 cells/L) at the time of the diagnosis, and The patient is 1 to 10 years old. High-risk ALL patients can have either of the following criteria: The WBC count ≥ 50,000 cells/mm3 (50.0 x 109 cells/L) at the time of the diagnosis, or The patient is younger than 1 year or older than 10 years (15).

Hyperglycemia was defined as more than one glucose value of ≥ 200 mg/dl during remission induction therapy (5). We used the ''GlucoSure Star'' brand glucometer for measuring patients' Blood glucose levels. Glucose levels were collected at the date of scheduled chemotherapy and as clinically indicated, and the frequency of blood glucose measurements varied for each patient based on their condition. Patients with a single glucose value of ≥ 200 mg/dl but repeated glucose values within 1 hr without intervention were < 200 mg/dl were not considered to have had hyperglycemia. Patients who had hyperglycemia during induction therapy and needed insulin to control blood sugar were selected as the case group.

The control group was selected from patients with leukemia who were matched with the case group in terms of risk, age, and sex, who did not develop hyperglycemia. Patients in both groups were compared in terms of remission, chemotherapy delay, length of hospital stay, and nosocomial infection. Survival rates of patients in the two groups were also compared after drug administration.

Complete remission was defined as bone marrow with less than 5% blasts and with the restoration of normal hematopoiesis (16-19).

Event-free survival (EFS) was defined as the length of time after primary treatment that the patient remains free of certain complications or events that the treatment was intended to prevent or delay.

Nosocomial infection was defined as clinical and paraclinical findings in favor of infection during hospitalization.

Response to initial treatment was considered as a blast of less than 5% in BMA (bone marrow aspiration) at the end of induction therapy. The final response was considered based on patients' initial 1 Year EFS rate.

Finally, the obtained data were analyzed using SPSS 21 software.

STATISTICAL METHODS

The obtained data are reported as mean ± standard error of the mean (± SEM). After entering the information in SPSS 21 software, central and dispersion indices, and charts were used to evaluate descriptive statistics.

In the inferential statistics section, the Independent sample t-test and the chi-square tests were used to analyze the two groups, and a P-value less than 0.05 was considered significant.

ETHICAL CONSIDERATION

The ethics committee of Arak University of Medical Sciences approved the study with a code of ethics (IR.ARAKMU.REC.1398.004).

RESULTS

DESCRIPTIVE ANALYSIS

Of the 192 patients included in the current study, 44 (22.91%) met previously defined criteria of hyperglycemia (random glucose level ≥ 200 mg/dl on > 1 measurement) during induction chemotherapy.

The descriptive demographic information of the patients is provided in Table 1, and The comparison of the prevalence of length of hospital stay, remission, chemotherapy delay, and survival of the patients is provided in Table 2.

Table 1. The descriptive demographic information of the patients

Patients	Age(y)	Gender(%)	Risk(%)
Case	Mean(±SEM): 8.25(±0.36) Min-Max: 2-14	Male: 30(68.18%) Female: 14(31.82%)	Standard risk: 28(63.63%) High risk: 16(36.37%)
Control	Mean(±SEM): 7.89(±0.26) Min-Max: 2-18	Male: 88(59.45%) Female: 60(40.55%)	Standard risk: 98(66.22%) High risk: 50(33.78%)

Comparing the two groups in terms of age, using the Independent Sample T-test showed that there is no significant statistical difference between the two groups (P-value = 0.50). Also, a comparison of the two groups in terms of gender using the Chi-square test showed that the two groups did not have a statistically significant difference (P-value = 0.30).

We used the Independent Sample T-test to Compare the two groups in terms of the length of hospital stay, and it was found that the two groups have a statistically significant difference (Figure 1 - P-value = 0.002 **).

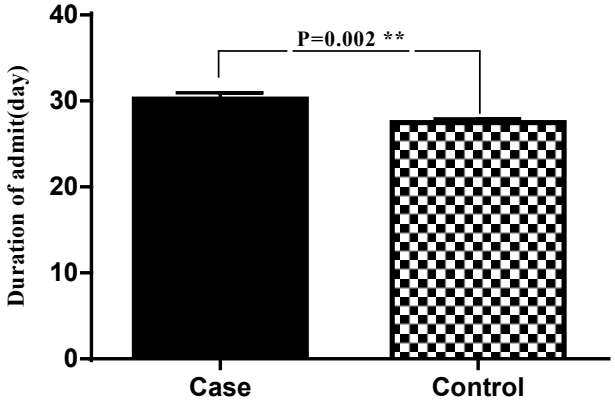

Figure 1. Comparison of the hospitalization time in two groups.

Comparing the two groups in terms of nosocomial infections using the Chi-square test showed that the two groups have a statistically significant difference (Figure 2 - P-value = 0.02).

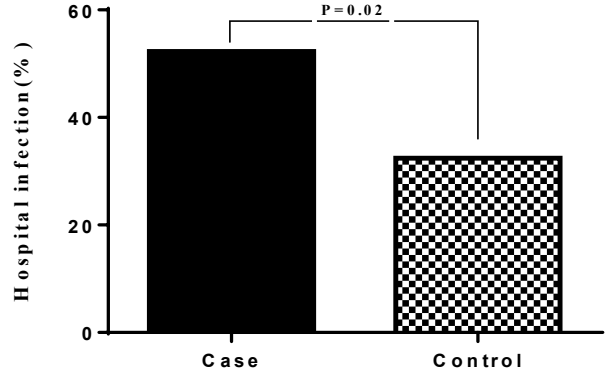

Figure 2. Comparison of the prevalence of nosocomial infections in the two groups

We found that all children with leukemia in the case group had a 15-day and one-month remission, but in the control group, all patients showed a 15-day remission, and only 2 (1.3%) did not have a 30-day remission.

By using the chi-square test, we found that the two groups did not have a significant difference in terms of 15 and 30 days Remission (Table 2- P-value = 0.56), but in terms of delay in chemotherapy, there was a statistically significant difference (Table 2- P-value = 0.01).

Comparison of survival in the two groups using the Chi-square test showed that there was no statistically significant difference between the two groups in terms of one-year (P-value = 0.80) and three-year (P-value = 0.90) survival (Table 2).

Table 2: The comparison of the prevalence of length of hospital stay, remission, chemotherapy delay, and survival of patients in case and control group

	Case	Control	P-Value
Mean (±SEM) length of hospital stay	30.23 (±0.71)	27.49 (±0.42)	0.002
Remission	15 days: 44(100%) 30 days: 44(100%)	15 days: 148(100%) 30 days: 146(98.7%	0.50
Chemotherapy delay	Positive: 23(52.28%) Negative: 21(47.72%)	Positive: 47(31.75%) Negative: 101(68.25%)	0.02
1-year EFS	Positive: 39(88.64%) Negative: 5(11.36%)	Positive: 128(86.48%) Negative: 20(13.52%)	0.80
3-year EFS	Positive: 37(84.09%) Negative: 7(15.91%)	Positive: 123(83.10%) Negative: 25(16.9%)	0.90

SEM: standard error of the mean, EFS: event-free survival

DISCUSSION

In this study, we investigated The effect of hyperglycemia during induction chemotherapy on the prognosis of pediatric patients with ALL, and the results showed that leukemic children who experienced hyperglycemia during therapy faced significantly more length of hospital stay, delay in chemotherapy, and nosocomial infections than others. Also, hyperglycemia did not affect 15 and 30-day remission rates and one and three-year EFS in children with leukemia.

Regarding the prevalence of hyperglycemia among ALL patients under induction chemotherapy, in a 2015 study (20), conducted over 12 years (1997-2008) on 133 Taiwanese children under 18 with leukemia, 16.5% of children with leukemia had hyperglycemia and diabetes during their treatment. Another study by Rona Y. Sonabend et al. (21), evaluated 167 children with ALL in Texas between the years (1999-2002), and the results showed that the prevalence of hyperglycemia was 34%. Julianne M Dare et al. (22), examined the effect of hyperglycemia on the risk of infection and premature death during treatment in 144 children with ALL. They found that the prevalence of hyperglycemia in children with leukemia under chemotherapy was 36%. A 2014 study (23), evaluated 159 leukemic children and reported a higher prevalence of hyperglycemia in children older than 10. However, in our study, which was conducted over 9 years (2009-2017) and evaluated 192

children with leukemia, 22.91% of children showed hyperglycemia. The discrepancy in the prevalence of diabetes between various studies is probably related to the different sample sizes as well as racial differences.

In terms of survival and remission rate, in Rona Y. Sonabend's study (21), leukemic children with hyperglycemia had a lower five-year survival rate than children with normal blood glucose. While our study indicated no difference in one and three-year survival. This difference is probably due to the difference in the duration of survival in the two studies, as well as genetic factors. A study by JR Roberson et al. (24), showed that overall survival (OS) was not different in patients with hyperglycemic and non-hyperglycemic leukemia. Another 2014 study (23), reported that the remission rate of diabetic and non-diabetic patients was not different. At the same time, the five-year survival was lower in children with hyperglycemia than in children with normal blood glucose.

Nosocomial infection is another notorious complication of hyperglycemia in ALL patients. Storey and Von Ah (25), examined 42 hospitalized patients with ALL and found no difference between hyperglycemic and non-hyperglycemic patients in terms of nosocomial infection. It is in contrast to our study, in which leukemic patients with high blood glucose faced more infections. Moreover, in Susan Storey's study, the length of hospital stay in hyperglycemic patients was longer than in patients with normal blood glucose, which confirms the results of our study. Mary Ann Weiser et al. (26), also found that the rate of nosocomial infection in ALL patients with hyperglycemia was higher than in patients with normal blood glucose.

We believe ALL children undergoing chemotherapy can be at high risk for hyperglycemia due to various factors, which necessitates further controlled studies to determine the extended and long-term complications. It can be the result of specific chemotherapeutic agents used during the induction phase and acute stress during the disease (5, 7, 27-37).

Despite several previously published studies, the true prevalence of hyperglycemia during induction chemotherapy is still unknown. This is because of the different methods used for evaluating the glycemic status and may be related to sample size, and also and racial factors in prior studies.

However, the proportion of patients who need insulin therapy during their induction chemotherapy for ALL is fairly consistent throughout studies in the literature.

Perhaps one of the shortcomings of our study is that we retrospectively reviewed the patients' clinical records to obtain their plasma glucose levels, which may not reflect the full picture of dysglycemia. We also could have benefited from using patients' HbA1c levels, but Given the nature of the study, it was not achievable.

It is unclear whether the patients who developed mild or moderate hyperglycemia and didn't need insulin therapy during induction chemotherapy are still at higher risk for adverse outcomes.

On the other hand, patients who need insulin to resolve their severe persistent hyperglycemia during induction chemotherapy are more likely to be at a higher risk for further complications.

CONCLUSION

In conclusion, there is a need for further studies to recognize patients at higher risk for developing hyperglycemia during chemotherapy. We need to determine standardized guidelines and protocols for monitoring hyperglycemia and insulin initiation and whether these interventions impact patients' outcomes.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

ABBREVATIONS

ALL; acute lymphoblastic leukemia, NCI; National Cancer Institute, OS; Overall survival.

REFERENCES

1. Howlader N, Noone A, Krapcho M, Neyman N, Aminou R, Waldron W, et al. SEER Cancer Statistics Review, 1975–2008. Bethesda, MD: National Cancer Institute; 2011. Also available online Last accessed December. 2011;1.
2. Redaelli A, Laskin B, Stephens J, Botteman M, Pashos C. A systematic literature review of the clinical and epidemiological burden of acute lymphoblastic leukaemia (ALL). European journal of cancer care. 2005;14(1):53-62.
3. Pizzo PA, Poplack DG. Principles and practice of pediatric oncology: Lippincott Williams & Wilkins; 2015.
4. Iyer R, Rao S, Pai S, Advani S, Magrath I. L-asparaginase related hyperglycemia. Indian Journal of cancer. 1993;30(2):72-6.
5. Lowas SR, Marks D, Malempati S. Prevalence of transient hyperglycemia during induction chemotherapy for pediatric acute lymphoblastic leukemia. Pediatric blood & cancer. 2009;52(7):814-8.
6. Alves C, Chaves C, Souza M. Transient diabetes mellitus related to L-asparaginase therapy. Arquivos Brasileiros de Endocrinologia & Metabologia. 2007;51(4):635-8.
7. Pui C-H, Burghen GA, Bowman WP, Aur RJ. Risk factors for hyperglycemia in children with leukemia receiving L-asparaginase and prednisone. The Journal of pediatrics. 1981;99(1):46-50.
8. Spinola-Castro AM, Siviero-Miachon AA, Andreoni S, Tosta-Hernandez P, Macedo C, Lee M. Transient hyperglycemia during childhood acute lymphocytic leukemia chemotherapy: an old event revisited. Clin Adv Hematol Oncol. 2009;7(7):465-72.
9. Baillargeon J, Langevin AM, Mullins J, Ferry Jr RJ, DeAngulo G, Thomas PJ, et al. Transient hyperglycemia in Hispanic children with acute lymphoblastic leukemia. Pediatric blood & cancer. 2005;45(7):960-3.
10. Wang Y, Chu H, Shu S, Chi C. Hyperglycemia induced by chemotherapeutic agents used in acute lymphoblastic leukemia: report of three cases. Zhonghua yi xue za zhi= Chinese medical journal; Free China ed. 1993;51(6):457-61.
11. McCormick MC, Sharp E, Kalpatthi R, Zullo J, Gurtunca N, Zhang J, et al. Hyperglycemia Requiring Insulin during ALL Induction Chemotherapy Associated with Increased Adverse Outcomes and Healthcare Costs. Pediatric blood & cancer. 2020;67(9):e28475.
12. Aisyi M, Andriastuti M, Kurniati N. The effect of combination of steroid and L-asparaginase on hyperglycemia in children with acute lymphoblastic leukemia (ALL). Asian Pacific journal of cancer prevention: APJCP. 2019;20(9):2619.
13. Demedis J, Scarbro S, Suresh K, Maloney K, Forlenza GP. Hyperglycemia and Other Glycemic Measures Throughout Therapy for Pediatric Acute Lymphoblastic Leukemia and Lymphoma. Journal of Pediatric Hematology/Oncology. 2023;45(2):e154-e60.
14. Tamaddoni A, Alijanpour M, Mahmoodi H, Miladi B, Bijani A, Assadollahi E, et al. The incidence of hyperglycemia during the induction phase of chemotherapy in patients with acute lymphoblastic leukemia. Iranian Journal of Pediatric Hematology & Oncology. 2019.
15. Ribeiro R, Pui C. Prognostic factors in childhood acute lymphoblastic leukemia. Hematologic pathology. 1993;7(3):121-42.
16. Kishi S, Griener J, Cheng C, Das S, Cook EH, Pei D, et al. Homocysteine, pharmacogenetics, and neurotoxicity in children with leukemia. Journal of Clinical Oncology. 2003;21(16):3084-91.
17. Pui C, Relling M, Sandlund J, Downing J, Campana D, Evans W. Rationale and design of Total Therapy Study XV for newly diagnosed childhood acute lymphoblastic leukemia. Annals of hematology. 2004;83:S124-6.

18. Pui C-H, Mahmoud HH, Rivera GK, Hancock ML, Sandlund JT, Behm FG, et al. Early intensification of intrathecal chemotherapy virtually eliminates central nervous system relapse in children with acute lymphoblastic leukemia. Blood, The Journal of the American Society of Hematology. 1998;92(2):411-5.
19. Pui C-H, Sandlund JT, Pei D, Campana D, Rivera GK, Ribeiro RC, et al. Improved outcome for children with acute lymphoblastic leukemia: results of Total Therapy Study XIIIB at St Jude Children's Research Hospital. Blood. 2004;104(9):2690-6.
20. Tsai M-C, Huang H-H, Chou Y-Y, Cheng C-N, Chen J-S, Lin S-J. Risk factors for hyperglycemia during chemotherapy for acute lymphoblastic leukemia among Taiwanese children. Pediatrics & Neonatology. 2015;56(5):339-45.
21. Sonabend RY, McKay SV, Okcu MF, Yan J, Haymond MW, Margolin JF. Hyperglycemia during induction therapy is associated with poorer survival in children with acute lymphocytic leukemia. The Journal of pediatrics. 2009;155(1):73-8.
22. Dare JM, Moppett JP, Shield JP, Hunt LP, Stevens MC. The impact of hyperglycemia on risk of infection and early death during induction therapy for acute lymphoblastic leukemia (ALL). Pediatric blood & cancer. 2013;60(12):E157-E9.
23. Zhang B-H, Wang J, Xue H-M, Chen C. Impact of chemotherapy-related hyperglycemia on prognosis of child acute lymphocytic leukemia. Asian Pacific Journal of Cancer Prevention. 2014;15(20):8855-9.
24. Roberson JR, Spraker HL, Shelso J, Zhou Y, Inaba H, Metzger ML, et al. Clinical consequences of hyperglycemia during remission induction therapy for pediatric acute lymphoblastic leukemia. Leukemia. 2009;23(2):245-50.
25. Storey S, Von Ah D. Prevalence and impact of hyperglycemia on hospitalized leukemia patients. European Journal of Oncology Nursing. 2015;19(1):13-7.
26. Weiser MA, Cabanillas ME, Konopleva M, Thomas DA, Pierce SA, Escalante CP, et al. Relation between the duration of remission and hyperglycemia during induction chemotherapy for acute lymphocytic leukemia with a hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone/methotrexate–cytarabine regimen. Cancer: Interdisciplinary International Journal of the American Cancer Society. 2004;100(6):1179-85.
27. Asensio C, Muzzin P, Rohner-Jeanrenaud F. Role of glucocorticoids in the physiopathology of excessive fat deposition and insulin resistance. International Journal of Obesity. 2004;28(4):S45-S52.
28. Belgaumi AF, Al-Bakrah M, Al-Mahr M, Al-Jefri A, Al-Musa A, Saleh M, et al. Dexamethasone-associated toxicity during induction chemotherapy for childhood acute lymphoblastic leukemia is augmented by concurrent use of daunomycin. Cancer: Interdisciplinary International Journal of the American Cancer Society. 2003;97(11):2898-903.
29. Carmona-Bayonas A, Font C, Ayala de la Peña F. Stress-induced hyperglycemia is a valuable biomarker in febrile neutropenia. Revista brasileira de hematologia e hemoterapia. 2013;35:12-4.
30. Carpentieri U, Balch MT. Hyperglycemia associated with the therapeutic use of L-asparaginase: possible role of insulin receptors. The Journal of pediatrics. 1978;93(5):775-8.
31. Cetin M, Yetgin S, Kara A, Tuncer AM, Günay M, Gümrük F, et al. Hyperglycemia, ketoacidosis and other complications of L-asparaginase in children with acute lymphoblastic leukemia. Journal of medicine. 1994;25(3-4):219-29.
32. Faustino EV, Apkon M. Persistent hyperglycemia in critically ill children. The Journal of pediatrics. 2005;146(1):30-4.
33. Hijiya N, Van Der Sluis IM. Asparaginase-associated toxicity in children with acute lymphoblastic leukemia. Leukemia & lymphoma. 2016;57(4):748-57.
34. Howard SC, Pui C-H. Endocrine complications in pediatric patients with acute lymphoblastic leukemia. Blood reviews. 2002;16(4):225-43.
35. Koltin D, Sung L, Naqvi A, Urbach SL. Medication induced diabetes during induction in pediatric acute lymphoblastic leukemia: prevalence, risk factors and characteristics. Supportive Care in Cancer. 2012;20(9):2009-15.
36. McMahon M, Gerich J, Rizza P. Effects of glucocorticoids on carbohydrate metabolism. Diabetes/metabolism reviews. 1988;4(1):17-30.
37. Srinivasan V, Spinella PC, Drott HR, Roth CL, Helfaer MA, Nadkarni V. Association of timing, duration, and intensity of hyperglycemia with intensive care unit mortality in critically ill children. Pediatric Critical Care Medicine. 2004;5(4):329-36.

Author Contribution: All authors have contributed in this study.
Funding statement: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
Acknowledgements: The authors are thankful to the staff of AmirKabir Hospital for their assistance with this project.