Serum Hepcidin Level in Patients with Acute Lymphoblastic Leukemia (ALL) during The Treatment Phase Their Effects on Erythropoisis Activity and Iron Reserves

by I Nyoman Wande

Submission date: 23-Apr-2021 02:11PM (UTC+0800)
Submission ID: 1567407534
File name: se_Their_Effects_on_Erythropoisis_Activity_and_Iron_Reserves.pdf (380.44K)
Word count: 2121
Character count: 11941

ISSN 0975-2366
DOI: https://doi.org/10.31838/ijpr/2020.12.03.049

Research Article

Serum Hepcidin Level in Patients with Acute Lymphoblastic Leukemia (ALL) during The Treatment Phase: Their Effects on Erythropoisis Activity and Iron Reserves

I NYOMAN WANDE[1*], YETTI HERNANINGSIH[2], KETUT ARIAWATI[3], PAULUS NOTOPUROBUDIONO[4], NI MADE LINAWATI[5], PANDE PUTU AYU PATRIA DEWI[6]
[1,6]Department of Clinical Pathology, Faculty of Medicine, Udayana University,
[2,4]Department of Clinical Pathology, Faculty of Medicine, Airlangga University,
[3]Department of Pediatric, Faculty of Medicine, Udayana University,
[5]Department of Histology, Faculty of Medicine, Udayana University, Indonesia
*Corresponding Author
Email ID: nyoman_wande@unud.ac.id
Received: 13.03.20, Revised: 11.04.20, Accepted: 10.05.20

ABSTRACT
Hepcidin levels increased significantly with increased of iron stores in early phase of acute leukemia patients when erithropoisis pressed by blast cells in bone marrow, then decreased significantly with acute leukemia remission. The study aimed to determine role of hepcidin in activity of erythropoisis and serum iron reserves in acute lymphoblastic leukemia (ALL) patients during phase of therapy. This study used an observational analytic design. Serum hepcidin examination used ELISA methods. Erythropoisis activity was determined by complete blood and reticulocyte percentage. Iron reserves was determined by serum iron and ferritin levels by ECLIA. Result shows a total of 48 patient subjects were divided into groups of induction, consolidation and maintenance phase with an average age of 6.81 years (induction), 9.7 years (consolidation) and 7.8 years (maintenance). In the normality test with Shapiro-Wilk data showed abnormal distribution ($p < 0.05$). Analysis by the Kruskal-Wallis test showed there were differences between the three treatment phases in the examination of hemoglobin, reticulocytes, serum iron, ferritin and hepcidin ($p < 0.05$). In statistical analysis with Spearman's rank correlation shows there is a significant correlation between hemoglobin with ferritin ($r = -0.416$, $p = 0.003$), hemoglobin with hepcidin ($r = -0.305$, $p = 0.035$), reticulocytes with hepcidin ($r = -0.496$), $p = 0.000$) and serum iron with hepcidin ($r = -0.302$, $p = 0.037$). We concluded that the higher levels of hepcidin indicate lower levels of hemoglobin, reticulocytes and serum iron in patients with acute lymphoblastic leukemia during treatment phase.

Keywords: Hepcidin, Acute Lymphoblastic Leukemia, Erythropoisis.

INTRODUCTION

Hepcidin is a peptide hormone which has function as antimicrobial. The liver synthesized it in response to stimulation of inflammation and excess iron. The first discovered of hepcidin was in human serum and urine. Initially it was isolated from the ultrafiltrates of plama and also called as liver expressed antimicrobial peptides (LEAP-1), then isolated from human urine and named hepatic antimicrobial peptide (HAMP). Currently this hormone named as Hepcidin because it comes from the liver, and has a bactericidal effect in vitro [1]. Hepcidin is activated as a negative regulator of intestinal absorption and release by macrophages. Hepcidin binds to the feroportin receptor and causes internalization and degradation of feroportin and iron retention in erythrocytes. This condition causes decreased absorption and mobilization of iron storage from the liver and macrophages. Hepcidin synthesis will increase when transferin saturation is high (when the transfer capacity binds to maximum serum iron), on the contrary hepcidin synthesis increases to low transferrin saturation compilation [2]. The expression of hepcidine is stimulated when the iron reserves increase is mainly caused by inflammation, otherwise it is expressed that it will be inhibited by anemia / hypoxia and increased urge erythropoisis. Damage regulators as a role in the pathogenesis of several diseases including anemia in malignancies. In this pathological situation, antagonistic signals to the regulation of hepcidin will occur simultaneously. At present there is little information about the expression of hepcidin in acute leukemia [3].

The production of hepcidin is regulated by three factors namely iron status, inflammatory stimuli such as interleukin 6 and unknown erythropoysis

signals. All of these factors can be found in acute lymphoblastic leukemia (ALL) [4]. Iron metabolism and erythropoisis are very closely related, iron metabolism imbalances show an association with several malignancies including leukemia [5,6]. Ferritin serum is a reliable marker for storage of body iron in most body conditions both physiological and pathological. However, ferritin is also an acute phase reactant that increases in inflammatory states [7].

MATERIAL AND METHODS

This study was an observational analytic design with cross-sectional design. This research was conducted in the Pediatric Inpatient Room at Sanglah Hospital and Clinical Pathology Laboratory, Medical Faculty, Udayana University in March-August 2019. Inclusion criteria of subjects: Age less than 18 years, was diagnosed with acute lymphoblastic leukemia (ALL) and underwent chemotherapy. Exclusion criteria: Patients coma or complications during treatment, relapse, and the presence of impaired liver function (increase in SGOT and SGPT 10x the normal limit). The sample size in this study were 48 patients, which were divided into three groups: induction, consolidation and maintenance phases. Serum hepcidin examination using the ELISA double antibody sandwich method Bio Assay Technology Laboratory®. Complete blood count and reticulocyte examination using a hematology analyzer Cell-Dyn Ruby® Abbot Laboratory. Serum iron and ferritin were examined by ECLIA method with Cobas e601.
This study has been received ethical approval by Ethics Committee of Udayana University, Bali, Indonesia.

Statistical Analysis

Normality test was performed with Shapiro-Wilk. Kruskal-Wallis test was conducted to determine the differences between the three groups of phases. Spearman's rank correlation analysis was performed to determine the relationship between the variables studied. Statistical analysis using SPSS version 14.

RESULTS AND DISCUSSION

Results

The total sample of the study was 48 patients divided into three groups: induction, consolidation and maintenance phase. The following below are characteristics of research subjects.

Table 1: The Characteristics of Subjects based on Research Groups

Characteristics	Induction phase	Consolidation phase	Maintenance phase
Mean of age (year)	6.81	9.7	7.8
Sex (Men/Women)	9/7	12/4	10/6
SGOT (U/l)	25.67 ± 11,80	24.78 ± 13.94	32.51 ± 9.01
SGPT (U/l)	34.31 ± 19.97	30.59 ± 21.09	33.05 ± 9.94
Hemoglobin (g/dl)	10.36 ± 1.35	10.27 ± 1.97	12.30 ± 1.28
Reticulocyte (%)	0.90 ± 0.51	2.76 ± 2.08	2.76 ± 1.79
Serum Iron (µg/dl)	79.50 ± 25.68	123.18 ± 73.61	156.92 ± 89.95
Ferritin (ng/ml)	1353.07 ± 1189.38	1758.26 ± 2020.00	749.77 ± 917.00
Hepcidin (pg/ml)	7545.17 ± 5271.99	1728.86 ±4042.83	210.88 ± 228.16

The results of this study indicate that hemoglobin levels during the treatment phase indicate that higher levels are in the maintenance phase. The same situation was shown in reticulocyte examination, there was an increase in reticulocyte levels during the consolidation and maintenance phases. Iron in the serum increases during the treatment phase. On the other hand, the levels of serum ferritin and hepcidin decrease during the treatment phase.

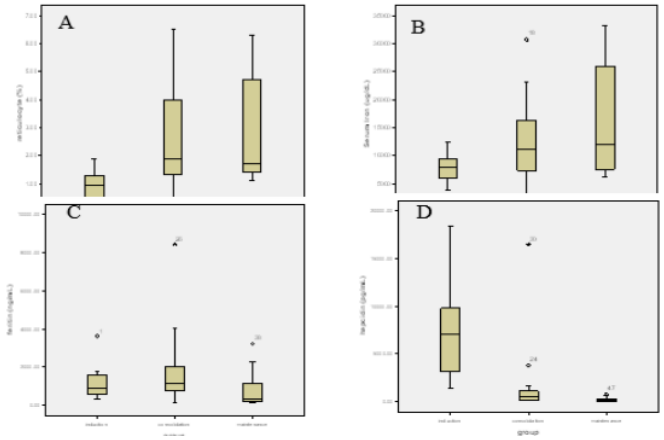

Fig.1: Plot diagram in the treatment group. A. Reticulocyte examination. B. Serum Iron Examination.

C. Ferritin Examination. D. Hepcidin examination

In the statistical test to determine the differences between the treatment phases of each examination parameter using the Kruskal-Wallis test showed a significant difference between the treatment phase groups both in hemoglobin, reticulocyte, serum iron, ferritin and hepcidin levels ($p < 0.05$). The statistical analysis with spearman's rank correlation showed that there was a significant relationship between hemoglobin and ferritin levels ($r = -0.416$, $p = 0.003$), hemoglobin with hepcidin ($r = -0.305$, $p = 0.035$), percentage of reticulocytes with hepcidin levels ($r = -0.496$, $p = 0.000$), serum iron with hepcidin levels ($r = -0.302$, $p = 0.037$).

DISCUSSION

The results of research conducted by Cheng et al. in 2011, stated that hepcidin levels increased significantly with an increase of iron reserves in early phase of acute leukemia patients, when the erythropoisis is suppressed by blasts cells in the bone marrow, then decreases significantly with acute remission of leukemia, whereas soluble transferrin receptor (sTfR) increases. There is an inverse relationship between serum hepcidin and erythropoisis markers such as red blood cells, hemoglobin, reticulocytes and sTfR. A positive correlation was found between hepcidin and ferritin, between hepsidin and the sideroblast ratio, and between hepsidin and interleukin 6 [8].

The results in this study are consistent with research conducted by Cheng et al 2011, in which the presence of higher hepcidin levels in the induction phase compared to the consolidation and maintenance phases. There is an inverse relationship between hepcidin levels with percentages of reticulocytes, hemoglobin and serum iron. The higher levels of hepcidin indicate the lower response of bone marrow erythropoisis. The low response of bone marrow erythoropoisis could be caused of the destruction of stem cells and bone marrow stroma, then impact on the function and number of blood cells [9].

Serum hepcidin has a negative correlation with hemoglobin levels which is consistent with what was reported by other studies. In the maintenance group LLA patients also showed higher levels of hepcidin compared to the normal group [3]. The hyperleucocytosis is associated with the lower of Hb levels. It was stated that lower hemoglobin levels or severe anemia at the time of diagnosis might be in accordance with the condition of further disease. It is possible that patients with higher Hb levels or mild anemia are detected in the early stages of the disease more sensitive to chemotherapy interventions [10].

The inbalances of iron metabolism are associated with several cancers including leukemia. Lipocalin 2 (LCN2) is an iron transporter and its function is related to iron metabolism and immune response. Type 2 Hydroxy Butyrate Dehydrogenase (BDH2) is a rate limiting factor in mammalian siderophore biogenesis. Siderophor bond with LCN2 can move iron between the cytoplasm and mitochondria. Higher rates of leukemia transformation are seen among patients with high BDH2 expression, and BDH2 mRNA expression correlates with serum ferritin levels. The function of BDH2 and LCN2 in leukemia may depend on intracellular iron concentrations [6].

CONCLUSION

Based on the above results and discussion can be drawn conclusions as follows: There was a high serum hepcidin level in the initial phase of

treatment (induction phase). There was an inverse relationship between serum hepcidin levels with hemoglobin, reticulocyte and serum iron levels during the treatment phase.

ACKNOWLEDGEMENT

The author would like to thank to the members of researchers who have helped conduct the study. The authors also thank to the Udayana University on **DIPA PNBP**, which has **funded** this research and others who have supported this research (ketut adi santika and other staf of clinical pathology laboratory, sanglah hospital denpasar).

REFERENCES

1. Park CH, Valore EV, Waring AJ, Ganz T. Hepsidin, a urinary antimicrobial peptide synthesized in the liver. J Biol Chem. 2001; 276 : 7806-10
2. Ganz T and Nemeth E. Iron imports. IV. Hepsidin and regulation of body iron metabolism. Am J Physiol Gastrointest Liver Physiol. 2006; 290: 199-203.
3. Ragab SM, Safan MA, Tayel SI, Genena SE, Ghanayem NM. Serum hepsidin level evaluation in children with acute lymphoblastic leukemia during different treatment phases; the influence of erythroid activity and iron stores. Clin Cancer Investig J. 2016; 5: 25-31.
4. Kanda, J. et al. (2008) 'Serum hepcidin level and erythropoietic activity after hematopoietic stem cell transplantation', Haematologica, 93(10), pp. 1550–1554. doi: 10.3324/haematol.12399.
5. Nemeth E. Iron regulation and erythropoiesis. Curr Opin Hematol. 2008; 15: 169-75.
6. Yang WC. Iron metabolism and leukemia. Adv Tech Biol Med. 2015; 3: 122.
7. Cook JD, Flowers CH, Skikne BS. The quantitative assessment of body iron. Blood. 2003; 101: 3359-64.
8. Cheng PP, Sun ZZ, Jiang F, Tang YT, Jiao XY. Hepsidin expression in patients with acute leukaemia. Eur. J. Clin. Investig. 2011; 42(5): 517-25.
9. Wande, I. N., Robi, M. and Hadi, S. (2019) 'The Correlation between total lymphocyte count , hemoglobin levels , lymphocyte / leukocyte ratio (LLR), and lymphocyte / neutrophil ratio (LNR) to CD4 levels in patients with Human Immunodeficiency Virus infection at Sanglah Hospital', 8(2), pp. 337–341. doi: 10.15562/bmj.v8i2.1408.
10. Teuffel O, Stanulla M, Cario G, Ludwig WD, Rottgers S, Schafer BW, Zimmermann M, Schrappe M, and Niggli FK. Anemia and survival in childhood acute lymphoblastic Leukemia. Haematologica. .2008; 93(11): 1652-57.

Serum Hepcidin Level in Patients with Acute Lymphoblastic Leukemia (ALL) during The Treatment Phase Their Effects on Erythropoisis Activity and Iron Reserves

ORIGINALITY REPORT

13%	10%	8%	0%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	docplayer.net Internet Source	2%
2	Aysel Uysal Derbent, Serap Aynur Simavli, Ikbal Kaygusuz, Ilknur Inegol Gumus, Saynur Yılmaz, Melehat Yıldırım, Sema Uysal. "Serum hepcidin is associated with parameters of glucose metabolism in women with gestational diabetes mellitus", The Journal of Maternal-Fetal & Neonatal Medicine, 2013 Publication	1%
3	gimsr.gitam.edu Internet Source	1%
4	iugspace.iugaza.edu.ps Internet Source	1%
5	www.karger.com Internet Source	1%
6	www.balimedicaljournal.org Internet Source	1%

7	dyuthi.cusat.ac.in Internet Source	1 %
8	I Wayan Weta, Wayan P Sutirtayasa, Wayan C Sucipta, Safarina G Malik, A.A.Ngurah Subawa, I Putu Eka Widyadharma. "Supplementation of Low Ratio n-6:n-3 PUFA Reduces Body Fatness in Young Obese Balinese Women: A Randomized Study with Optimized Energy Regulation", Current Research in Nutrition and Food Science Journal, 2020 Publication	1 %
9	D Kusnadi, M N I Liwang, S Katu, A H Mubin, R Halim. "Correlation between the neutrophil-lymphocyte count ratio and bacterial infection in patient with human immunodeficiency virus", IOP Conference Series: Earth and Environmental Science, 2018 Publication	1 %
10	iovs.arvojournals.org Internet Source	1 %
11	Xi Huang, Eric T. Fung, Christine Yip, Anne Zeleniuch-Jacquotte. "Serum prohepcidin is associated with soluble transferrin receptor-1 but not ferritin in healthy post-menopausal women", Blood Cells, Molecules, and Diseases, 2008 Publication	1 %

12	Mehmet Muhittin Yalcin, Alev Eroglu Altinova, Mujde Akturk, Ozlem Gulbahar et al. "GDF-15 and Hepcidin Levels in Nonanemic Patients with Impaired Glucose Tolerance", Journal of Diabetes Research, 2016 Publication	<1 %
13	"FREE COMMUNICATIONS POSTER COMMUNICATIONS", Nephrology, 6/2005 Publication	<1 %
14	Aryeh Shander. "Clinical consequences of iron overload from chronic red blood cell transfusions, its diagnosis, and its management by chelation therapy : IRON OVERLOAD FROM CHRONIC TRANSFUSION THERAPY", Transfusion, 01/15/2010 Publication	<1 %
15	I. Gusti Ngurah Made Suwarba, Soetjiningsih Soetjiningsih, I. Made Bakta, I. Made Jawi et al. "Supplementation of Water Extract of Purple Sweet Potato (Ipomoeo Batatas L) in Improving the EEG Image, Decreasing the Seizure Frequency and Reducing the Frequency of Drugs Resistant of Focal Epilepsy in Children", Biomedical and Pharmacology Journal, 2019 Publication	<1 %
16	link.springer.com Internet Source	<1 %

17	www.biomedcentral.com Internet Source	<1%
18	Rudi Wisaksana, Quirijn de Mast, Bachti Alisjahbana, Hadi Jusuf et al. "Inverse Relationship of Serum Hepcidin Levels with CD4 Cell Counts in HIV-Infected Patients Selected from an Indonesian Prospective Cohort Study", PLoS ONE, 2013 Publication	<1%

Exclude quotes	On	Exclude matches	Off
Exclude bibliography	On		

Serum Hepcidin Level in Patients with Acute Lymphoblastic Leukemia (ALL) during The Treatment Phase Their Effects on Erythropoisis Activity and Iron Reserves

GRADEMARK REPORT

FINAL GRADE

/100

GENERAL COMMENTS

Instructor

PAGE 1

PAGE 2

PAGE 3

PAGE 4