7-2015

# Clinical Utility of Lactate Dehydrogenase in Determining the Severity of Hemolysis in Sickle Cell Anemia.

Samir K. Ballas
*Thomas Jefferson University*

# Lactate dehydrogenase, hemolysis, hyperhemolysis, and hydroxyurea in sickle cell anemia

Samir K. Ballas, Department of Medicine, Cardeza Foundation for Hematologic Research, Jefferson Medical College, Thomas Jefferson University, Philadelphia PA

Correspondence:
Samir K. Ballas MD, FACP, FASCP
Cardeza Foundation
1020 Locust Street
Philadelphia, PA 19107
Phone: 856-745-6380
Fax: 856-795-0809
E-mail: samir.ballas@jefferson.edu

Number of words: 642
Number of references: 8
Number of pages: 4

**To the editor:**

The interesting letter to the editor by Mecabo et al.[1] sheds new perspective on the correlation of lactate dehydrogenase (LDH) and hemolysis in patients with sickle cell anemia (SCA). Their data show that LDH-3 seems to be the isoenzyme that is correlated with hemolysis. Accordingly, LDH-3 could be a useful marker in future studies to determine the source of elevated levels of serum LDH in patients with SCA as well as in other diseases. Expense, insurance approval and clinical availability, however, may hamper its availability on a routine basis. Moreover and unlike previous reports,[2,3] Mecabo et al.[1] found that hydroxyurea (HU) did not show reduction of LDH or other hemolytic parameters in patients with SCA taking HU. Lactate dehydrogenase-3, however, was decreased in patients with SCA taking HU.

Given the above new information, I wish to clarify two issues pertinent to this controversial subject. Since sickle cell disease (SCD) is a hemolytic disorder, all its variants have variable degrees of hemolysis and, hence, have variable degrees of elevated LDH levels that are most severe in SS. In a subset of patients with SCA and uncomplicated vaso-occlusive crises (VOC) a hyperhemolytic state was characterized by 40% decrease in the mean red blood cell (RBC) $t_{1/2}$ survival determined by $^{51}Cr$ method, 53% decrease in total cell life, 54% increase in the destructive rate of RBC with a significant 58% increase in LDH and changes in other parameters of hemolysis compared to steady state values.[4] The mean or median levels in patients with hemolysis or hyperhemolysis are usually < 1000 U/L.[1,4] Levels of LDH > 1000 U/L suggest additional sources of the enzyme with or without hemolysis or hyperhemolysis especially if other parameters of hemolysis are absent. Such high levels of LDH could be a sign of co-existent tissue damage due to SCA. Elevated levels of LDH are also known to be markers of testicular germ cell tumors and of melanoma. [5] In stage 3 testicular cancer the LDH value could be more than 10 times the upper limit of the reference range. [6] Moreover, in multiple myeloma (MM) a high level of LDH is a poor prognostic sign despite the fact that hemolysis is not an issue in MM.[7] Similarly, it would be instructive to use the LDH values or, even better, the LDH-3 values to rate the severity of hemolysis and the presence or absence of organ damage in SCD.

The second issue pertains to the effect of HU on the hemolytic parameters in patients with SCA. We have prospectively studied the erythropoietic activity in patients with SCA before and after treatment with HU.[8] Some of the patients were enrolled in the double-blind placebo controlled trial of HU in patients with SCA (also known as the MSH study) and others were enrolled in an open label study. Determinants of erythropoietic activity included, among other things, hemoglobin (Hb), mean corpuscular volume (MCV), reticulocyte count, Hb F, RBC survival by the $^{51}$Cr method, RBC life span and RBC production/destruction rate. As shown in Table 1 responders to HU showed significant increase in MCV, Hb F, RBC survival, cell life and in the production/destruction rate and significant decrease in the reticulocyte count. Non-responders to HU and the placebo group showed no difference before and after HU therapy. Moreover there was positive significant correlation between Hb F level and RBC survival. The study by Mecabo et al[1] did not analyze the hemolytic parameters in terms of clinical response to HU and of Hb F level that, apparently, was not determined. Furthermore, the authors stated that the hemolytic parameters in the HU group were not statistically different from the SS group that did not receive HU. Accordingly, it seems that the majority of the patients taking HU were nonresponders and that may explain why the trial have failed to show the beneficial effects of HU on RBC survival.

## References


1. Mecabo G, Yamamoto M, Biassi TP, Figueiredo MS. Lactate dehydrogenase isoenzyme 3 and hemolysis in sickle cell anemia: a possible correlation? *Blood*. 2015;125(24):3821-3822.
2. Steinberg MH, McCarthy WF, Castro O, et al. The risks and benefits of long-term use of hydroxyurea in sickle cell anemia: A 17.5 year follow-up. *Am J Hematol*. 2010;85(6):403-408.
3. Voskaridou E, Christoulas D, Bilalis A, et al. The effect of prolonged administration of hydroxyurea on morbidity and mortality in adult patients with sickle cell syndromes: results of a 17-year, single-center trial (LaSHS). *Blood*. 2010;115(12):2354-2363.
4. Ballas SK, Marcolina MJ. Hyperhemolysis during the evolution of uncomplicated acute painful episodes in patients with sickle cell anemia. *Transfusion*. 2006;46(1):105-110.
5. Jialal I, Devaraj S, Bettaieb A, Haj F, Adams-Huet B. Increased adipose tissue secretion of Fetuin-A, lipopolysaccharide-binding protein and high-mobility group box protein 1 in metabolic syndrome. *Atherosclerosis*. 2015;241(1):130-137.
6. Compton CC, Byrd DR, Garcia-Aguilar J, Kurtzman SH, Olawaiye A, Washington MK. Testis. In: Compton CC, Byrd DR, Garcia-Aguilar J, Kurtzman SH, Olawaiye A, Washington MK, eds. AJCC Cancer Staging Handbook 7th ed. New York, NY: Springer; 2010:539-546.

7. Kiba T, Ito T, Nakashima T, et al. Bortezomib and dexamethasone for multiple myeloma: higher AST and LDH levels associated with a worse prognosis on overall survival. *BMC Cancer*. 2014;14:462.
8. Ballas SK, Marcolina MJ, Dover GJ, Barton FB. Erythropoietic activity in patients with sickle cell anaemia before and after treatment with hydroxyurea. *Br J Haematol*. 1999;105(2):491-496.