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Thesis Abstract

Oxidative stress in sickle cell patients: influence of haplotypes and specific medication

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The main cause of sickle cell disease (SCD) is a single β-globin gene mutation that leads to the unusual hemoglobin (Hb) called Hb S with characteristics that differ from those of normal Hb. SCD is characterized by a multifaceted pathophysiology, which involves multiple changes in sickle erythrocytes, vaso-occlusive episodes, hemolysis, inflammatory mediator activation, oxidative stress, and endothelial cell dysfunction. Therefore, there is a decreased blood flow and microcirculation obstruction leading to anemia, pain crises and multiple organ failure. Since an excess of reactive oxygen species is cytotoxic, modifying various cellular mechanisms and, thus, causing organ damage, the aim of this study was to assess the antioxidant capacity and oxidative stress in SCD, correlating with patient genotype, β-globin cluster haplotypes and specific medication. In a longitudinal study, SCD patients were evaluated at two times: for time one (T1), 69 blood samples and for time two (T2), 55 blood samples. The patients were from the São José do Rio Preto Blood Bank (SJRP) and São Paulo Santa Casa Medical School Blood Center (SP). Electrophoretic, chromatographic and molecular assays were performed for SCD genotyping and β-globin cluster identification, including biochemical measurements for determination of thiobarbituric acid reactive species (TBARS) and Trolox equivalence antioxidant capacity (TEAC). Through SCD genetic characterization, we found a high frequency of Hb SS in both groups. There was a higher frequency of Hb S/β-thalassemia interaction in SJRP (10.9%) with the typical Mediterranean mutation CD39 and IVS-I-110. For the Hb S allele, the Bantu haplotype was the most frequent in both groups (60.6%). We found a patient with the Cameroon haplotype, rare in the Brazilian population; 9.8% of evaluated samples showed an atypical haplotype, one of them with *Xmn*I polymorphism, giving the patient 15.8% fetal Hb and minimal clinical manifestations. For the β-thalassemia allele, haplotype II was associated with the CD39 mutation, and haplotype I with IVS-I-110. The best response to medication/specific treatment for the oxidative process at both T1 and T2 was observed in the use of hydroxyurea combined with deferasirox (DFX). Patients undergoing transfusion therapy and the use of DFX, after an average exposure of 381.8 days to DFX, showed a decrease in transferrin saturation index ($P = 0.001$), serum iron ($P < 0.01$), total iron binding ($P = 0.01$), and as a

consequence, a decrease in lipid peroxidation (P = 0.04). Patients without specific medication showed an increase in lipid peroxidation (P = 0.03) and decrease in antioxidant capacity (P = 0.02) based on longitudinal evaluation. Also in this group, we found a positive linear correlation between TBARS values and monocyte count (T1: r = 0.81, P = 0.02 and T2: r = 0.82, P = 0.02) and between higher TEAC values and a greater leukocyte number (T1: r = 0.81, P = 0.02 and T2: r = 0.82, P = 0.02). The serum iron increase in transfused patients within 60 days of sampling was associated with an increase of 35% (P = 0.02 and R^2 = 0.35) in TBARS values. This study represents the first longitudinal evaluation of the oxidative profile in SCD patients, considering genotype, haplotype and different therapeutic approaches in Brazil.

Key words: Sickle cell disease; TBARS; TEAC; Hydroxyurea; Deferasirox