Changes in Transcranial Doppler Flow Velocities in Children with Sickle Cell Disease: The Impact of Hydroxyurea Therapy

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Background and Objectives: Hydroxyurea (HU) was recently described as a substitute for chronic transfusion for children with sickle cell disease (SCD) and abnormal transcranial Doppler (TCD) velocities who have received at least 1 year of transfusions. However, the role of HU in reverting elevated TCD velocities in patients not treated with transfusion is still debatable. The objective of the study was to examine whether HU influences the progression of TCD velocities in children with SCD. *Patients and Methods:* Children with SCD with at least 2 TCDs not less than 6 months apart were evaluated over 51 months. Time-averaged maximum mean (TAMM) velocities for the initial and the last transcranial Doppler examinations were noted and differences compared between HU and HU-naive groups. *Results:* Overall, 68.8% of the HU-group with elevated TCD velocities compared with 40.0% of the HU-naive experienced TCD reversal (P = .047). A higher proportion of the HU-naive group, 7 (14.3%) versus 9.8% of the HU group experienced TCD conversion. Those with initial conditional velocities in the HU-group experienced a significant reduction in TAMM velocities (from 176.8 ± 5.3 to 162.7 ± 13.9 cm/s, difference of 14.1 cm/s; P = .001) unlike those in the HU-naive group (176.3 ± 5.3 to 170.0 ± 18.6 cm/s, difference of 6.3 cm/s; P = .148). The change in the TAMM velocities was also significantly higher among the HU-group (14.1 ± 12.4 cm/s versus 6.3 ± 18.5 cm/s, P = .015). *Conclusion:* Our data suggest a beneficial role of HU in TCD velocity reduction in patients not treated with chronic transfusions, particularly among those with initial conditional TCD velocities. **Key Words:** Children—chronic blood transfusions—hydroxyurea—sickle cell disease—transcranial Doppler.

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Introduction

Stroke is a major complication of sickle cell disease (SCD), even in very young children.[1,2] The incidence of stroke in SCD was reported as .61-.76 events per 100 patient-years.[3] About 11% of children with homozygous sickle cell anaemia (SS) develop stroke by the end of the second decade of life, with the majority of the events occurring between the ages of 2 and 9 years.[4,5] The underlying etiology in most cases is an ischemic stroke caused by large-vessel stenosis or occlusion.[2]

Transcranial Doppler (TCD) ultrasonography, a recommended routine screening test to identify children at high risk of developing stroke, measures flow velocities within large intracranial arteries. TCD should be routinely performed in children between 2 and 16 years, the age group at the highest risk of sickle cerebral vasculopathy and stroke. Although the prevalence of abnormal TCD findings in SCD from previous series varies, especially if either first-ever or follow-up exams are reported,[5-7] it is generally believed that 5%-10% of these children have abnormal TCD velocities, whereas up to 20% may have conditional velocities.[8] Studies have also shown that between 29% and 55% of children with conditional TCD velocities will develop abnormal TCD (conversion) and 1%-3% of these children may eventually develop stroke because they are given no specific treatment apart from close observation and repeated TCD examination.[9,10] Although about 10% of children with abnormal TCD findings may develop stroke, chronic blood transfusion (CBT) can reduce the risk by 90%.[8,10,11]

For about 30 years, especially in high-income countries, hydroxyurea (HU) has been in use to manage patients with SCD with clinical and laboratory markers of severe and chronic organ dysfunction. Since then, clinical experience and several studies have clearly depicted its efficacy and relative safety, to the extent that HU is currently accepted as a major approach directly linked to improved life span, quality of life, lower costs and rate of treatment, reduced disease severity, and attendant morbidities and mortality.[12]

Treatment with HU increases the production of hemoglobin F, reduces the total white blood cell count and the absolute neutrophil and platelet counts, and improves hemoglobin levels and erythrocyte rheological characteristics.[13,14] In addition, HU had been described as a substitute for chronic transfusions for high-risk children with SCD and abnormal TCD velocities who have received at least 1 year of transfusions.[15] A long-term cohort study in France showed that transfusions could be stopped in patients with SCD who are switched to HU after achieving a normal TCD velocity. The authors, however, warned that the switch (from transfusions to HU) should be done with caution, with a strict quarterly TCD follow-up and an immediate reintroduction of transfusion in case of reversal. In that report, although 45 patients with normalized velocities on transfusions were switched to HU, 28% of them experienced reversal back to abnormal TCD before the age of 9.5 years even though they were on a maximum tolerated dose.[16]

Individual response to HU is unpredictable and its ability to reverse end-organ failure associated with SCD is yet to be established. Although HU has been reported to decrease TCD velocities,[5,17] its role in reverting abnormal and conditional TCD velocities to normal velocities in patients not treated with transfusion therapy has been scarcely investigated. Therefore, we examined whether HU as the main therapy was associated with changes in TCD flow velocities and reversal of abnormal and conditional TCD velocities to normal velocities in children with SCD.

Patients and Methods

Study Location

This retrospective comparative study was carried out at the Paediatric Hematology and Neurovascular Units, Escola Paulista de Medicina, Universidade Federal de São Paulo, Brazil. The Paediatric Hematology unit offers comprehensive SCD care including the use of HU and a CBT program when indicated. The Neurovascular Unit of the hospital also performs routine TCD examinations weekly on children with SCD.

Study Population

The study population included children between the age of 2 and 16 years with SCD who had TCD examination from February 2011 to April 2015. Only children with hemoglobin SS or hemoglobin Sβ-thalassemia who had at least 2 TCDs in not less than 6 months apart were included. Those on CBT and those whose intervals between the initial transcranial Doppler (TCDI) and the last transcranial Doppler TCDL or duration of HU therapy was less than 6 months were not included. Institutional approval was obtained from the Ethics and Research Committee of the hospital.

Demographics and Clinical Assessment of Patients with SCD

Data on sociodemographics and clinical history (medical history and physical findings) were obtained for each patient by a review of relevant medical charts and the electronic data bank of the hospital. The use and the duration of the use of HU were noted for each patient.

HU Therapy

Clinical and laboratory data were used to initiate children on HU in line with the Brazilian guidelines for the use of HU in SCD.[18] Common indications included a frequent, significant vaso-occlusive crisis (at least 3 episodes per year), a recurrent acute chest syndrome; 1 episode