Brazilian Guidelines for transcranial doppler in children and adolescents with sickle cell disease

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Background: Sickle cell disease is the most common monogenic hereditary disease in Brazil. Although strokes are one of the main causes of morbidity and mortality in these patients, the use of transcranial Doppler to identify children at risk is not universally used.

Objective: To develop Brazilian guidelines for the use of transcranial Doppler in sickle cell disease children and adolescents, so that related health policies can be expanded, and thus contribute to reduce morbidity and mortality.

Methods: The guidelines were formulated in a consensus meeting of experts in transcranial Doppler and sickle cell disease. The issues discussed were previously formulated and scientific articles in databases (MEDLINE, SciELO and Cochrane) were carefully analyzed. The consensus for each question was obtained by a vote of experts on the specific theme.

Results: Recommendations were made, including indications for the use of transcranial Doppler according to the sickle cell disease genotype and patients age; the necessary conditions to perform the exam and its periodicity depending on exam results; the criteria for the indication of blood transfusions and iron chelation therapy; the indication of hydroxyurea; and the therapeutic approach in cases of conditional transcranial Doppler.

Conclusion: The Brazilian guidelines on the use of transcranial doppler in sickle cell disease patients may reduce the risk of strokes, and thus reduce the morbidity and mortality and improve the quality of life of sickle cell disease patients.

Keywords: Ultrasonography, doppler, transcranial/methods; Anemia, sickle cell/diagnosis; Anemia, sickle cell/therapy; Hemoglobin, sickle; Stroke/prevention & control; Child; Adolescent; Guideline

Introduction

Sickle cell disease (SCD) is the most common monogenic hereditary disease in Brazil occurring predominantly among African descents.¹ (A) The term SCD includes sickle cell anemia (SCA) the form of the disease that occurs in homozygotes of hemoglobin S (Hb SS), as well as pathological conditions caused by combinations of the hemoglobin S gene with other hereditary hemoglobin disorders such as sickle cell SC disease, Hb S/B+ thalassemia and Hb S/ß0 thalassemia. Complications of SCD, such as renal failure, vaso-occlusive crisis, acute chest syndrome and strokes result in a reduction of 25 to 30 years of life expectancy of SCD patients compared to the general population.² (B)

Recently, several aspects have contributed significantly to the reduction in mortality in SCD patients. These include the control of infections through immunization and the prophylactic use of antibiotics during early life; watchfulness and appropriate guidance for parents or caregivers to recognize early signs of splenic sequestration; the diagnosis and treatment of acute chest syndrome; and the identification of children at risk for developing strokes using transcranial doppler (TCD), combined with early use of packed red blood cell (RBC) transfusions when test results are abnormal.³ (D)

HEMORIO, with the support of the Ministry of Health in Brazil, the Associação Brasileira de Hematologia e Hemoterapia, and the Pro-HEMORIO Foundation, decided to develop the Brazilian guidelines on the use of transcranial doppler in sickle cell disease patients with the intention of expanding health policies for SCD and to contribute in reducing morbidity and mortality resulting from this pathology. This work was developed in line with the National Newborn Screening Program which guarantees universal access of newborns to screening for hemoglobinopathies, and Government decree 1391, which establishes guidelines for the National Policy of Comprehensive Care for People with Sickle Cell Disease and other Hemoglobinopathies in the Brazilian national healthcare service.³ (D)
Methods

A committee of specialists was formed and the guidelines were formulated in two parallel consensus meetings. At a consensus meeting of experts on TCD, nine regional facilitators, reference physicians in their regions on this theme, discussed the technical issues of the procedure. Four national facilitators, physicians who are recognized as experts in these sub-themes, presented the issues and the supporting scientific evidence. Records of the debate and a final summary of the findings for each question were entrusted to two other specialists in TCD. The consensus meeting was attended by experts in SCD, 26 regional facilitators who discussed technical matters involving the indication of TCD and the treatment to be adopted depending on the different findings of TCD.

The issues discussed at both consensus meetings were previously formulated by the national facilitators and two coordinators of the event, all nationally renowned physicians. Before the meeting, the national facilitators and coordinators were also responsible for the identification of regional facilitators assigned to each theme as well as the selection and distribution of publications to all participants. The scientific papers were identified from the MEDLINE, SciELO and Cochrane databases and papers were classified according to the degree of recommendation and level of evidence. The following designations were adopted: (A) highly consistent experimental or observational studies; (B) less consistent experimental or observational studies; (C) case reports (uncontrolled studies); (D) opinions without critical assessment based on consensus, physiologic studies or animal models. The consensus for each question was obtained by voting and proposals were accepted even if there was a maximum of three opposing votes. Abstentions were not considered opposing votes. All participants had the right to vote, except for five participants of organizations that represent SCD carriers.

Results

Genotype of hemoglobinopathies

Recommendation: TCD should be used for primary prevention of strokes in SCD patients, regardless of the genotype of the disease, but with priority to those with the Hb SS and Hb S/ß0thalassemia genotypes.

Although the incidence of strokes is higher in patients with the Hb SS genotype, it should be noted that strokes also occur in patients with other genotypes. According to a publication of the Cooperative Study of Sickle Cell Disease Group, the incidence of strokes (number of acute events/100 patients/year) is 0.61 for patients with Hb SS, 0.17 for Hb SC, 0.11 for Hb S/ß+ thalassemia and 0.10 for Hb S/ß0 thalassemia.

It is estimated that 11%, 15% and 24% of SCA patients and 2%, 4% and 10% of Hb SC patients develop symptomatic strokes up to the ages of 20, 30 and 45 years old, respectively. The acute event may occur spontaneously or after any acute complication such as, for example, infections. Additionally, the study showed that the estimated prevalence of strokes adjusted for age was 4.01% in patients with Hb SS; 2.43% in Hb S/ß0 thalassemia, 1.29% for Hb S/ß+ thalassemia and 0.84% for Hb SC.6,9 (B)

Given these data, it was deemed appropriate to recommend TCD as a method of primary prevention for all SCD patients regardless of genotype. The long-term monitoring of the population might allow for eventual determination of various intervals between examinations according to the genotype of the disease, as well as a reassessment of the necessity of screening for genotypes with lower risk, such as Hb SC and Hb S/ß+ thalassemia.

Age of patients

Recommendation: TCD should be used for primary prevention of strokes in SCD patients aged between two and 16 years of age.

In the publication of the Cooperative Study of Sickle Cell Disease Group, the overall incidence of the first stroke among SCD patients was 0.08 acute events/100 patients/year in under two-year olds; 0.75 in patients between two and five years old, 0.55 between six and nine years old, 0.30 between 10 and 19 years old, and 0.45 between 20 and 29 years old.9 (B) Although over 16-year-old SCD patients may be at increased risk of strokes, the association between flow velocity measured by TCD and the risk of strokes was first demonstrated in the cohort of SCD patients from the Medical College of Georgia, which involved children between three and 18 years old.14,15 (B)

Subsequently the study, Stroke Prevention Trial in Sickle Cell Anemia (STOP), which included patients with SCA aged between two and 16 years, confirmed the predictive value of TCD for strokes in this patient population.9 (A) and demonstrated that blood transfusions significantly reduced the risk of strokes among children in this age range with abnormal TCD.7,8 (A) Moreover, these studies established their own parameters for the definition of abnormal TCD in this cohort of patients.6,7 (A) Given the fact that the cerebral blood flow (CBF) and the estimated speed of this flow (CBFV) measured by TCD, are increased in anemic conditions due to decreased oxygen transport capacity of the blood, it was shown that the parameters of TCD related to stenosis in adults could not be applied to SCD children, because of the age and the anemia itself.9 (B)10,11,12 (C)13 (D)

Thus, considering the relatively low risk of strokes in under 2-year-old children with SCD; the absence of validated parameters of abnormal TCD in SCD patients of < 2 years old and > 18 years old; and lack of evidence to support transfusion therapy in SCA patients with ages > 16 years, the consensus recommendation is to perform TCD for primary prevention in patients aged between two and 16 years old.
Frequency of transcranial doppler

Recommendation: Conventional TCD is the method of choice and should be repeated frequency according to the criteria listed in table 1. The examination must be conducted and interpreted in accordance with the parameters set by the STOP study. The examination should be performed with the patient awake, afebrilie and at least four weeks after acute events and blood transfusions.

Although the parameters in the STOP study were arbitrarily defined, the risk categories proved to be excellent for the stratification of risk of strokes and the decision to start transfusion therapy. Thus we recommend the adoption of the STOP study protocol for the indication of TCD as a primary stroke prevention method in SCD patients. TCD may vary due to individual physiological factors (such as sleep, for example) and pathological factors (such as fever, for example) that increase the CBFV, which is the reason that it is recommended to defer examinations for four weeks in such cases.

TCD based on the methodology adopted in the STOP study included insonation of 15 arterial segments of the Circle of Willis: the M1 segment of the middle cerebral artery (MCA) and to check its entire length at 2-mm intervals to the bifurcation; the bifurcation of the internal carotid artery (ICA); the distal or terminal ICA, anterior cerebral artery, posterior cerebral artery, in both transtemporal windows; and the basilar artery (top or its bifurcation) through the transforaminal window. The predictive risk factor for strokes according to the STOP study was determined by the mean maximum speed of the CBFV at the bifurcation and distal ICA bilaterally. Wave spectral information was not used in the STOP study and the submandibular and transorbital windows were not evaluated. Some clinical studies provide regression equations to convert the speed of blood flow from TCD imaging to corresponding conventional TCD velocities and that very low speeds (< 70 cm/s) may be indicative of severe stenosis, which is the reason that it is recommended to repeat the examination after one month, or to examine the image by medical criteria.

In addition, the meeting considered that it is essential to use educational interventions to target parents and caregivers as well as children, about the importance of conducting systematic TCD examinations as well as the need for different therapeutic interventions for those at high risk for strokes.

Conventional TCD versus TCD imaging

As mentioned previously, conventional TCD is the method of choice for primary stroke prevention in SCD patients and the test should be performed and interpreted in accordance with the parameters set by the STOP study. TCD imaging techniques were not investigated in the STOP study. However, a few scientific papers have been published using TCD imaging that tried to evaluate and establish possible correlations between the findings using this method and data obtained with conventional TCD. It was observed that the velocities obtained by TCD imaging ranged from values similar to conventional TCD to values 20% lower and this variation depended on the insonation angle.

Thus, the meeting considered that there is not enough scientific evidence to make any recommendation of cutoff values for TCD imaging. Services and Institutions that only have TCD imaging must take into account differences in speeds that are reported in the literature. Some clinical studies provide regression equations to convert the speed of blood flow from TCD imaging to corresponding conventional TCD velocities and

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Table 1 - Recommendations for the frequency of TCD according to the result of the examination

| Result of TCD | CBFV (cm/s) | Frequency of exam |
|--------------|-------------|-------------------|
| Absence of window | --          | Use other image resource to analyze the cerebrovascular event |
| Technical difficulty due to lack of cooperation | --          | Repeat every three months. We recommend evaluation by another examiner |
| Low CBFV      | < 70        | Repeat after 1 month |
| Normal CBFV   | < 170       | Repeat annually |
| Low conditional * | Between 170 and 184 | Repeat at three-month intervals. In the case of normal subsequent results, we should adopt the normal conduct for the group |
| High conditional * | Between 185 and 199 | Repeat after 1 month. In cases of unchanged examinations, it is recommended to repeat every three months. In cases of two consecutive abnormal results, it is recommended to discuss the risk of strokes and consider chronic transfusion regimen |
| Abnormal      | Between 200 and 219 | Repeat after 1 month. If the value remains ≥ 200, it is recommended to discuss the risk of strokes and consider chronic transfusion regimen. If the result decreases to 170-199, it is recommended to repeat in 1 month if high conditional (between 185 and 199); or 6 months if conditional low (between 170 and 184). If the result is normalized (<170), it is recommended to repeat in 1 year. |
|               | More than 220 | Discuss imminent risk of strokes and consider chronic transfusion regime |

TCD = Transcranial Doppler; CBFV = Cerebral blood flow velocity
thus compatible with those used in the STOP study. However, it must be remembered that such regression equations may not apply to all TCD imaging devices. It is recommended that the method employed (conventional TCD or TCD imaging) should be cited in the report of test results.

RBC transfusion and iron chelation

Recommendation: RBC transfusion regimens of three to six weeks using exchange transfusion or partial exsanguinous transfusion is indicated for patients who present at least two consecutive TCD examinations with average CBFV > 200 cm/s (Table 1). Phenotyping should be made for Kell, Kidd, Duffy and MNSs and when possible for the Lewis, P and Lutheran blood group systems. Always use samples leucocyte depleted RBC and phenotyped RBCs, in principle, for the ABO, Rh and Kell systems. It is recommended that the storage time of RBCs to be transfused does not exceed seven days and are negative for Hb S. The patient should be maintained with a maximum Hb level of up to 10 g/dL and pre-transfusion Hb level less than 50%.

Iron chelation therapy is indicated for patients submitted to a simple transfusion regimen who have received more than twenty units of packed red blood cells and who have serum ferritin concentrations greater than 1000 ng/mL (at least two measurements under normal conditions) or grade III or IV hepatic siderosis by liver biopsy or liver iron concentrations equal to 4 mg/gram dry matter or above by magnetic resonance imaging (MRI). The therapeutic alternatives include orally administered deferasirox and subcutaneously administered deferoxamine.

In the STOP study, 130 of the 1934 participants were 2- to 16-year-old children who had changed TCD (mean CBFV > 200 cm/s in one or both of the middle cerebral arteries or the distal segment of the internal carotid artery in two exams at an interval of at least two weeks). These children were randomized into two groups: observation (with occasional transfusions) and a regular transfusion regimen aiming at maintaining Hb S below 30%. After 20 months of follow up, there was one case of a stroke in the 63 children in the transfusion group versus 11 cases of strokes in 67 children in the observation group. These results indicate a 92% reduction in relative risk for the occurrence of strokes (reduction in the risk of strokes from 10% per year to < 1% per year). (17) (A) The follow-up of patients undergoing chronic transfusion regimens for primary prevention of strokes in the STOP study also showed significant reductions in the levels of free hemoglobin compared to controls not subjected to transfusion or only to occasional transfusions. Furthermore, other markers of hemolysis such as lactate dehydrogenase and alanine aminotransferase levels were reduced. It is believed that the increase in circulating hemoglobin and the reduction in hemolysis with consequent reductions in free hemoglobin plasma levels increase bioavailability of nitric oxide and its effects by reducing or preventing endothelial dysfunction, which would help to explain the role of transfusions in preventing strokes. (24) (A) Therefore, it is recommended to start packed red blood cell transfusions according to the TCD results as described in Table 1.

However, regular blood transfusion regimens can lead to an accumulation of iron in the body, as physiological mechanisms to excrete excessive iron are restricted. SCD Patients appear to suffer tissue damage similar to other populations of chronically transfused patients, including iron deposits in the liver, heart and endocrine organs. The therapeutic alternatives for iron chelation therapy in SCD patients undergoing blood transfusions include deferoxamine and deferasirox. (25) (A) (26) (B)

Indication of hydroxyurea

Recommendation: Although the exchange transfusion regimen is the method of choice for primary prevention of strokes in SCD patients who are indicated for this procedure, treatment with hydroxyurea (HU) may be indicated in cases in which Hb S levels can not be maintained < 50%, in cases of patients who do not comply to the red blood cell transfusion regimen, in cases of alloimmunization, in situations that phenotyped blood is unavailable and in children without intravenous access.

HU is an antimetabolite that blocks the synthesis of deoxyribonucleic acid by inhibiting ribonucleotide reductase. The efficacy of this agent in the treatment of SCD appears to be related to increased levels of hemoglobin F (which reduces the formation of hemoglobin S), cyto reduction of neutrophils, increased water content inside the RBCs, and increased capacity for deformation and improvement of microvascular flow of sickle erythrocytes. (27) (D)

Since the classic Multicenter Study of Hydroxyurea (MSH) study published in 1995 by Charach et al., (28) (A) and the data obtained by Steinberg et al. (29) (A) over more than nine years of follow-up of patients using HU, such as the reduction in the number and intensity of pain crises, decreased hospitalization and reduction in mortality, HU has been recommended in an ever increasing number of cases, not only for adults but for children from two years of age or even earlier.

These are cheap, easy-to-use oral medications with few serious adverse effects. However, one of the key issues is the use of the maximum tolerated dose, which can reach 35 mg/kg/day in order to obtain the best possible outcome.

One important issue regarding the use of HU is whether such treatment can prevent the occurrence and recurrence of strokes.

In a prospective study, 35 children who had suffered strokes discontinued their red blood cell transfusion regimens and started drug therapy with HU associated with serial phlebotomy to reduce iron overload. The study showed a reduction in the rate of recurrent strokes from 5.7 events/100 patient-years to 3.6 events/100 patient-years as well as reduction in iron overload evaluated by serum ferritin levels and liver biopsy. The authors concluded that HU partially...
prevents the occurrence of strokes and that serial phlebotomy is capable of preventing transfusional iron overload.\(^{(30)}\) (B) In a Belgian study on the use of HU in SCD children at high risk of strokes as detected by TCD, the CBFV decreased significantly in 11 of 34 children with abnormal TCDs, and only one developed a primary stroke over a follow-up of 96 patient-years.\(^{(19)}\) (B)

Due to this data there was a consensus in the meeting that HU therapy is an alternative to the blood transfusion regimen particularly in situations where patients do not comply with transfusion therapy.

**Therapeutic approach to conditional transcranial doppler**

Recommendation: There is no scientific evidence to recommend the use of HU in patients with conditional TCD.

The evaluation of the effects of HU on CBFV measured by TCD in SCA children showed that medication use at the maximum tolerated dose resulted in a significant decrease of the velocities. After a year of full-dose treatment, the following results were obtained from 15 children with conditional values of velocities; the velocity decreased in 14; the velocities dropped below 200 cm/s in five of six children with abnormal initial values at TCD and whose parents had refused treatment by transfusions.\(^{(31)}\) (B) In a cohort of 24 SCD patients, treatment with HU has shown to result in average reductions in CBFV of 13.0 cm/s at TCD imaging. Patients with untreated SCD constituted the control group adjusted for age, in which the CBFV showed an increase of 4.72 cm/s (significant difference, p <0.001). Of the five patients that HU therapy is an initiative of leading experts in the areas of diagnosis and treatment of SCD, with the participation of those responsible for public health agencies, national medical societies, and institutions that represent SCD patients. The adoption of these guidelines may result in a reduction in the risk of strokes in this patient population as demonstrated by scientific evidence, thereby helping to reduce morbidity and mortality and to improve quality of life of SCD patients.

**References**

1. Cançado RD, Jesus JA. Sickle cell disease in Brazil. Rev Bras Hematol Hemoter. 2007;29(3):203-6.
2. Platt OS, Brambilla DJ, Rosse WF, Milner PF, Castro O, Steinberg MH, et al. Mortality in sickle cell disease. Life expectancy and risk factors for early death. N Engl J Med. 1994;330(23):1639-44. Comment in: N Engl J Med. 1994;331(15):1022-3.
3. Ohene-Frempong K, Weiner SJ, Sleeper LA, Miller ST, Embury S, Mmohr JW, et al. Cerebrovascular accidents in sickle cell disease: rates and risk factors. Blood. 1998;91(1):288-94.
4. Adams RJ, McKie VC, Carl EM, Nichols FT, Perry R, Brock K, et al. Long-term stroke risk in children with sickle cell disease screened with transcranial Doppler Ann Neurol. 1997;42(3):699-704.
5. Adams R, McKie V, Nichols F, Carl E, Zhang DL, McKie K, et al. The use of transcranial ultrasonography to predict stroke in sickle cell disease. N Engl J Med. 1992;326(9):605-10. Comment in: N Engl J Med. 1992;326(9):637-9.
6. Adams RJ, Brambilla DJ, Granger S, Gallagher D, Vichinsky E, Abboud MR, Pegelow CH, Woods G, Rohde EM, Nichols FT, Jones A, Luden JP, Bowman L, Hagner S, Morales KH, Roach ES; STOP Study. Stroke and conversion to high risk in children screened with transcranial Doppler ultrasound during the STOP study. Blood. 2004;103(10):3689-94.
7. Adams RJ, McKie VC, Hsu L, Files B, Vichinsky E, Pegelow C, et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. N Engl J Med.1998;339(1):5-11. Comment in: N Engl J Med. 1998;339(20):1477-8.
8. Lee MT, Piomelli S, Granger S, Miller ST, Harkness S, Brambilla DJ, Adams RJ; STOP Study Investigators. Stroke Prevention Trial in Sickle Cell Anemia (STOP): extended follow-up and final results. Blood. 2006;108(3):847-52.
9. Brass LM, Pavlakis SG, DeVivo D, Piomelli S, Mohr JP. Transcranial Doppler measurements of the middle cerebral artery. Effect of hematocrit. Stroke. 1988;19(12):1466-9.
10. Sampaio Silva G, Vicari P, Figueiredo MS, Filho AC, Valadi N, Massaro AR. Transcranial Doppler in adult patients with sickle cell disease. Cerebrovasc Dis. 2006;21(1-2):38-41.
11. Valadi N, Silva GS, Bowman LS, Ramsingh D, Vicari P, Filho AC, et al. Transcranial Doppler ultrasonography in adults with sickle cell disease. Neurology. 2006;67(4):572-4.
12. Adams RJ. Big strokes in small persons. Arch Neurol. 2007; 64 (11):1567-74.
13. Adams C, Hwang PA, Gilday DL, Armstrong DC, Becker LE, Hoffman HJ. Comparison of SPECT, EEG, CT, MRI, and pathology in partial epilepsy. Pediatr Neurol. 1992;8(2):97-103.
14. Silva GS, Vicari P, Figueiredo MS, Carrete H Jr, Idagawa MH, Massaro AR. Brain magnetic resonance imaging abnormalities in adult patients with sickle cell disease: correlation with transcranial Doppler findings. Stroke. 2009;40(7):2408-12.
15. Katz ML, Smith-Whitley K, Ruzek SB, Ohene-Frempong K.
Knowledge of stroke risk, signs of stroke, and the need for stroke education among children with sickle cell disease and their caregivers. Ethn Health. 2002;7(2):115-23.

16. NHS Sickle Cell & Thalassaemia Screening Programme. TD Standards Writing Group of the Sickle Cell and Thalassaemia Screening Programme. Transcranial Doppler Scanning for Children with Sickle Cell Disease. Standards and Guidance. NHS; March 2009. [cited 2010 Oct 12]. Available from: www.sct.screening.nhs.uk

17. Jones A, Granger S, Brambilla D, Gallagher D, Vichinsky E, Woods G, et al. Can peak systolic velocities be used for prediction of stroke in sickle cell anemia? Pediatr Radiol. 2005;35(1):66-72.

18. Jones AM, Seibert JJ, Nichols FT, Kinder DL, Cox K, Luden J, et al. Comparison of transcranial color Doppler imaging (TCDI) and transcranial Doppler (TCD) in children with sickle-cell anemia. Pediatr Radiol. 2001;31(7):461-9. Comment in: Pediatr Radiol. 2002;32(9):690-1 reply 692-3.

19. Kratovil T, Bulas D, Driscoll MC, Speller-Brown B, McCarter R, Minniti CP. Hydroxyurea therapy lowers TCD velocities in children with sickle cell disease. Pediatr Blood Cancer. 2006;47(7):894-900.

20. Neish AS, Blews DE, Simms CA, Merritt RK, Spinks AJ. Screening for stroke in sickle cell anemia: comparison of transcranial Doppler imaging and non-imaging US techniques. Radiology. 2002;222(3):709-14.

21. Bulas DI, Jones A, Seibert JJ, Driscoll C, O'Donnell R, Adams RJ. Transcranial Doppler (TCD) screening for stroke prevention in sickle cell anemia: pitfalls in technique variation. Pediatr Radiol. 2000;30(11):733-8.

22. Krejza J, Rudzinski W, Pawlak MA, Tomaszewski M, Ichord R, Kwiatkowski J, et al. Angle-corrected imaging transcranial doppler sonography versus imaging and nonimaging transcranial doppler sonography in children with sickle cell disease. AJNR Am J Neuroradiol. 2007;28(8):1613-8.

23. Adams RJ. TCD in sickle cell disease: an important and useful test. Pediatr Radiol. 2005;35(3):229-34.

24. Lezcano NE, Odo N, Kutlar A, Brambilla D, Adams RJ. Regular transfusion lowers plasma free hemoglobin in children with sickle-cell disease at risk for stroke. Stroke. 2006;37(6):1424-6.

25. Vichinsky E, Onyekwere O, Porter J, Swardlow P, Eckert SV, et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. N Engl J Med. 1995;332(20):1317-22. Comment in: N Engl J Med. 1995;333(15):1008; author reply 1009. N Engl J Med. 1996;334(5):333-4. N Engl J Med. 1996;334(5):333. N Engl J Med. 1995;332(20):1372-4. N Engl J Med. 1995;333(15):1008-9.

26. Steinberg MH, Barton F, Castro O, Pegelow CH, Ballas SK, Kutlar A, et al. Effect of hydroxyurea on mortality and morbidity in adult sickle cell anemia: risks and benefits up to 9 years of treatment. JAMA. 2003;289(13):1645-51. Comment in: JAMA. 2003;289(13):1692-4. JAMA. 2003;290(6):752; author reply 754. JAMA. 2003;290(6):752-3; author reply 754. JAMA. 2003;290(6):753; author reply 754. JAMA. 2003;290(6):753-4; author reply 754.

27. Ware RE, Zimmerman SA, Sylvestre PB, Mortier NA, Davis JS, Teem WR, et al. Prevention of secondary stroke and resolution of transfusional iron overload in children with sickle cell anemia using hydroxyurea and phlebotomy. J Pediatr. 2004;145(3):287-8. J Pediatr. 2005;147(4):560-1.

28. Zimmerman SA, Schultz WH, Burgett S, Mortier NA, Ware RE. Hydroxyurea therapy lowers transcranial Doppler flow velocities in children with sickle cell anemia. Blood. 2007;110(3):1043-7. Comment in: Blood. 2008;111(2):963-4; author reply 964.

29. Gulbis B, Haberman D, Dufour D, Christophe C, Vermylen C, Kagambega F, et al. Hydroxyurea for sickle cell disease in children and for prevention of cerebrovascular events: the Belgian experience. Blood. 2005;105(7):2685-90.