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Clinical Alert from the National Heart, Lung, and Blood Institute

The National Heart, Lung, and Blood Institute (NHLBI) announced today an advisory recommending that blood transfusions should be continued in order to reduce the rate of strokes (cerebral infarctions or hemorrhages) in children with sickle cell anemia who are at risk of strokes. Strokes occur in approximately 10% of children with sickle cell anemia. These cerebral vascular events can be very debilitating, leading to physical and neuro-psychological impairment which can affect motor skills, school performance, and overall quality of life.

In 1997, a Clinical Alert was issued by NHLBI based on the Stroke Prevention Trial in Sickle Cell Anemia (STOP I) Trial. In that study, a 90% reduction in the rate of first-time stroke was reported when chronic blood transfusions were offered to children with sickle cell anemia who had been identified as being at high risk by transcranial Doppler (TCD). Periodic red blood cell transfusions reduced the rate of stroke by 90 % in STOP I. By lowering the level of hemoglobin S (Hb S) below 30%, strokes were prevented in children found to be at increased risk by virtue of having elevated transcranial doppler (TCD) velocities in the internal carotid and middle cerebral arteries.

In 2000, a second randomized, controlled clinical trial, STOP II, funded by NHLBI, was initiated to test whether chronic transfusions for primary stroke prevention could be safely discontinued after at least 30 months (range 30 - 91 months) in children who had not had an overt stroke, and who had reversion to low risk TCD velocity with chronic transfusion therapy. Low risk TCD velocity is defined as < 170 cm/sec time averaged mean of the maximum. The purpose of the STOP II trial was to optimize transfusion for stroke prevention by determining which children needed continued therapy to prevent stroke. Chronic blood transfusion therapy is costly and can be associated with significant morbidities including risk of iron overload, alloimmunization, and exposure to infectious blood borne agents.

The STOP II Trial showed that when transfusions were discontinued after a minimum of 30 months, a significant number of children reverted to high risk range of TCD velocities or, in the case of two children, developed an overt stroke after an elevated TCD velocity was observed.

The STOP II Trial, headquartered at the Medical College of Georgia (Dr. Robert Adams) and the New England Research Institutes (Dr. Donald Brambilla), enrolled 79 children who ranged from 2 to 18 years of age. The patients were drawn from 23 clinical centers in the United States and two in Canada (list attached). The patients were randomized to receive either standard supportive care with periodic blood transfusions or to be withdrawn from periodic blood transfusions if their TCD velocity had returned to low-risk range. Children with severe stenosis of the middle cerebral or internal carotid arteries viewed by magnetic resonance angiography

(MRA) were excluded from randomization. The primary endpoint was the comparison of the rate of reversion to abnormal TCD velocity and/or stroke in the treated and control groups.

In both treatment arms, children received close clinical and TCD surveillance for the first occurrence of reversion of TCD to abnormal, confirmed with two or more TCD's of 200 cm/sec or higher. This TCD change indicated a return of high risk for overt stroke. In addition, overt stroke was included as part of the primary endpoint. The main hypothesis was that over 3 years of observation fewer than 50% of children in the experimental arm would revert to high stroke risk or have an overt stroke, and that quarterly (at least every 8 to 12 weeks) surveillance with TCD would provide acceptable safety monitoring with respect to stroke risk.

The patients in the transfusion arm received periodic simple or exchange blood transfusions every 3 to 4 weeks in an effort to maintain the Hb S level below 30%. The trial protocol required that red blood cell transfusions were matched for ABO, C, D, E, and K antigens. The children in both arms were followed for exposure to transfusion transmitted viral diseases and iron overload. Patients who had been on the transfusion protocol and received a cumulative dose of 250 ml/kg of blood began to develop elevated serum ferritin levels greater than 2500 mg/L and were started on chelation therapy.

After 79 of a planned sample size of 100 children were randomized, the Data and Safety Monitoring Board, appointed by NHLBI, recommended closure of the study for safety concerns when an interim analysis showed a highly significant difference between the transfusion and non-transfusion treatment arms with respect to the composite endpoint of TCD reversion to high risk and overt stroke. At the time of closure of the trial, in 41 subjects randomized to come off transfusion, there had been 16 endpoints. Of the 16 endpoints, 14 reversions to high risk TCD (without stroke) occurred, and two ischemic strokes occurred shortly after the first TCD reverted to abnormal but before a confirmatory TCD could be obtained and transfusion therapy resumed. Six other subjects were returned to periodic transfusion therapy for clinical reasons before endpoints occurred (crossovers), primarily due to recurrent acute chest syndrome or sickle cell related painful episodes.

No neurologic events or reversions to high risk TCD were observed in those subjects who were in the chronic transfusion treatment arm. The reversions to abnormal TCD velocity were seen early after discontinuation of periodic transfusions, between 4-9 months. The length of time on transfusion therapy prior to randomization was the only potential indicator of TCD reversion to abnormal that was identified by secondary analyses. There was a trend toward lower risk of reversion to abnormal TCD in subjects who were transfused for greater than 54 months prior to randomization. Age, gender, presence of silent infarct lesions on magnetic resonance imaging, %Hb S on transfusion, and number of transfusions prior to randomization did not predict increased risk of reversion to abnormal TCD.

While some children tolerate removal from chronic transfusion therapy without apparent problems, discontinuation of transfusion after 30 months cannot be recommended based on STOP II due to the high TCD reversion rate, and the small risk of overt stroke despite frequent TCD surveillance. In addition, there is the likelihood that some children may need to return to transfusions for other sickle cell related clinical reasons.

It should be emphasized that the patients studied in STOP II were those with TCD velocities that reverted to low risk on periodic transfusions, and without severe arterial lesions on MRA. This

subset of children who participated in STOP II are thought to be at lower risk for stroke than those children who had been in STOP I but did not qualify for STOP II because their TCD velocities did not revert to normal on transfusions or because they had arterial lesions on MRA.

Further research will be needed to: (1) determine better ways to predict those who can be removed safely from transfusion while still accomplishing effective primary stroke prevention, or (2) identify and test alternative therapies to transfusion that will provide safe and effective protection from stroke with fewer side effects than transfusion. Physicians will have to carefully discuss with patients and their families the risk-benefit ratio of continuing periodic transfusions for stroke prevention when compared to the long term side effects of iron overload. The choice of clinical management, including whether to continue periodic transfusions or to stop transfusions with TCD monitoring every 2-3 months, must be made on a case-by-case basis. Children who continue on chronic transfusions should also receive appropriate management of iron overload.

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