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Reduction in TCD velocity after regular blood transfusion therapy is associated with a change in hemoglobin S fraction in sickle cell anemia

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Letter to the Editor:

Abnormal transcranial doppler ultrasound (TCD) velocity is a risk factor for stroke in children with sickle cell anemia (SCA). The STOP trial demonstrated that transfusions reduce TCD velocity and stroke risk[1]. However, neither STOP[1] nor STOP II[2] results reported the unit decline in hemoglobin S (HbS) fraction per unit change in TCD velocity. In a pooled analysis of 10 studies demonstrating the relationship between hydroxyurea and TCD measurements, the average drop in TCD velocity was 21 cm/s (95% confidence interval [CI], 14.8–29.0)[3] after hydroxyurea therapy. The pooled analysis did not demonstrate any change in the HbS fraction per unit change in TCD velocity. However, Hurlet-Jensen and colleagues demonstrated that a decline in HbS fraction has a more significant impact on cerebral blood flow (i.e. rate of blood delivery to tissue; ml/100g/min) than an increase in the total hemoglobin level[4]. Here, we tested the hypothesis that HbS fraction has a more significant impact on the TCD velocity than total hemoglobin in individuals with SCA.

SIT trial participants included children aged 5–15 years with a confirmed diagnosis of hemoglobin SS or hemoglobin $S\beta^0$ thalassemia; time-averaged maximum mean TCD velocity of the terminal portion of the internal carotid or the middle cerebral artery <200 cm/s by non-imaging technique, or time-averaged maximum velocity <185 cm/s by imaging technique; and no prior history of overt strokes or seizures. Inclusion criteria for this secondary analysis: 1) SIT trial participant randomized to regular transfusions; 2) completed

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CONTRIBUTION

LJ, MR, MJD, and MRD wrote the paper; MR performed the statistical analyses, MRD conceived the project and approach.

at least 10 transfusions; 3) at least two TCD exams completed, with the first TCD before the start of regular blood transfusion; 4) and the second TCD performed near to the time of transfusions; 5) HbS at baseline and at the time of follow-up TCD. Exclusion criterion: any neurological event during the SIT trial. The trial was approved by the Institutional Review Boards (IRB) at all participating institutions and registered at https://clinicaltrials.gov/ (NCT00072761). Informed consents were performed per local IRB procedures. Participant characteristics were described by median and interquartile range (IQR) for continuous measures and by number and percent for categorical measures. Multivariable mixed regression models of longitudinal change in TCD were constructed, with age and time as covariates, and separate models for hemoglobin S or total hemoglobin because of sample size. Based on the evidence that decreasing HbS fraction and increasing hemoglobin levels are associated with a decrease in TCD velocities[5], a two-sided p-value≤0.05 was considered statistically significant. Data analysis was performed using SPSS, version 26.0 (IBM, Armonk, New York).

From the randomized SIT cohort of 99 children who received approximately monthly blood transfusions, 50 completed at least ten transfusions and had at least two TCD exams. Of these 50, 24 had paired TCD measurements, with one excluded for a neurological event and one excluded for missing HbS value, thus 22 had the first TCD measurement before transfusion (median 2.2 months, IQR 0.8 – 3.7), and the second TCD measurement completed within a median −0.1 month (IQR −0.6 to 0.1 months) of the last transfusion. The median HbS fraction of 20.5% at the time of the second TCD measurement provides evidence that the participants had reached a steady-state of regular blood transfusion therapy when the goal was to keep the maximum HbS percentage less than 30%. The median interval between the first and the last TCD was 2.5 years.

After initiating transfusion therapy, TCD assessment was not performed as part of the trial protocol because the TCD measurement after initiating transfusion has not been associated with a future incidence rate of ischemic strokes[6]. All 22 children had HbS fraction available at the time of TCD and later when receiving regular blood transfusion therapy based on institutional practice. No statistically significant differences were observed between participants who completed at least ten transfusions (n=22) and participants with at least two TCD examinations but were not eligible for this analyses due to at least one exclusion criteria (n=23), Supplemental table 1.As expected, with transfusion, the median TCD velocity decreased from a median of 142.5 cm/sec to 112.0 cm/sec (p<0.001) while the median HbS fraction decreased from 89.0 to 20.5 (p<0.001) and the median hemoglobin levels increased from 7.5 g/dl to 9.4 gm/dL (p<0.001), Table 1. One participant that was excluded from the analyses had a paired TCD measurement before and after transfusions and developed an overt stroke. The participant's TAMMV TCD measurement before regular blood transfusion was initially 141 cm/sec and only decreased 7 cm/sec, to 134 cm/sec; the hemoglobin increased from 7.5 mg/d to 9.3 mg/dl and the HbS fraction went from 91.6 to 25.0 over 1.63 years.

A mixed multivariable linear regression model, with random intercepts, controlling for age at TCD and times between TCD measurements, Supplement table 2, found a 4.0 cm/sec reduction (95% CI 1.3 – 6.6) in TCD velocity for every 10% reduction in HbS% (p=0.004).

Thus, clinically when the HbS fraction is reduced from 90% to 20%, the minimum expected decline in TCD velocity is 9 cm/sec (−70%/10 × 1.3 cm/sec) and the median expected decline of 28 cm/sec (−70%/10 × 4 cm/sec). A separate mixed model found a 4.6 cm/sec reduction (95% CI −9.78 – 0.54) in TCD velocity for every 1 gm/dL increase in hemoglobin (p=0.078). Due to the small sample size, we were unable to include both the fraction of HbS and total hemoglobin in the same model. The small sample size may have contributed to the absence of a statistical association between change in total hemoglobin level and TCD velocity. Given the strong evidence that increasing hemoglobin levels are expected to decrease TCD measurements, a one tailed instead of a two test could have been applied. The one tailed T test would have been statistically significant demonstrating a relationship between increasing hemoglobin levels and p value of 0.039.

Similar to Hurlet-Jensen et al.[4], the current study demonstrated a significant relationship between HbS fraction and TCD velocity. However, Hurlet-Jensen used the Xenon inhalation method, an experimental measure to assess cerebral blood flow in three participants with serial evaluations of HbS fraction after cessation of regular blood transfusion therapy. In contrast, our study used TCD velocity, a standard clinical test, and included 22 participants with serial assessment of HbS fraction and total hemoglobin levels after starting regular blood transfusion therapy for a median of 2.5 years.

The optimal decline of TCD velocity after blood transfusion therapy, if any, that confers a low risk of future strokes after starting regular blood transfusion therapy is unknown. Typically, TCD velocity is not obtained after starting regular blood transfusion therapy because, as in the STOP II Trial, TCD velocity obtained after receiving regular blood transfusion therapy was not predictive of future ischemic strokes[7]. Potentially, comparing the expected to the observed decline of TCD velocities after starting regular blood transfusion or hydroxyurea therapy may help determine if there is an ongoing risk for ischemic strokes. However, in children with SCA, ischemic strokes are rare after starting regular blood transfusion therapy (0.24 per 100 patient-years (95% CI 0.18–0.31))[7]. Despite the low incidence rate of ischemic strokes with abnormal TCD measurements after blood transfusion therapy, in a large population of children with SCA, ischemic strokes will occur[7]. A limitation in our study is the small sample size of 22 paired TCD measurements before and after regular blood transfusion therapy for at least a year. Despite this limitation, our study is one of the first to compare cerebral hemodynamics prior to regular blood transfusion therapy and after the goal of transfusion therapy is reached, a hemoglobin S fraction less than 30%. Due to the high correlation of HbS and total hemoglobin (low HbS levels associated with high total hemoglobin levels) while receiving regular blood transfusion therapy, and the small sample size, both independent covariates were not included in a regression model. As a result of the collaborative efforts of our team with large cohorts of children being receiving primary stroke prevention therapies (DISPLACE trial NCT04173026, and SPRING trial, NCT02560935), in future studies, we will be able to test the hypothesis that the magnitude of the drop in TCD velocities after starting blood transfusion or hydroxyurea therapy predicts futures strokes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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CONFLICT OF INTEREST

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TABLE 1

Characteristics of the randomized SIT cohort (n = 22) that completed at least 10 transfusions and had at least two TCD examinations

Participant characteristic	Summary statistics
Time from first to last TCD (years), median (IQR)	2.5(1.7–3.3)
Number of TCD exams per patient, n (%)	
2	9 (40.9)
3	9 (4D.9)
4	4(18.2)
Age at first TCD (years), median (IQR)	10.8 (9.5–1 1.7)
Gender, male, N (%)	1.5 (68.2)
White blood cell count, baseline (k/mm^3), median (IQR)	13.2(11.0–14 6)
Reticulocyte (%), baseline median (IQR)(n = 20)	12.3 (10.0–15.2)
Hemoglobin at first TCD [g/dL), median (IQR)	7.5 (6.3–8.2)
Hemoglobin at last TCD (g/dL), median (IQR)	9.4 (3.4–9.9)
Hemoglobin S at first TCD (%), median (IQR)	89.0 (84.8–94.0)
Hemoglobin S at last TCD (%), median (IQR)	20.5 (1 0.5–32.3)
First TCD (cm/s), median (IQR)	142.5(125.2–173.0)
Last TCD (cm/s), median (IQR)	112.0(97.8–139.2)