Cerebral Oximetry in Ugandan Children With Severe Anemia
Clinical Categories and Response to Transfusion

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IMPORTANCE Severe anemia, defined as a hemoglobin level of less than 5.0 g/dL, affects millions of children worldwide. The brain has a high basal demand for oxygen and is especially vulnerable to hypoxemia. Previous studies have documented neurocognitive impairment in children with severe anemia. Data on cerebral tissue oxygenation in children with severe anemia and their response to blood transfusion are limited.

OBJECTIVE To measure hemoglobin saturation in cerebral tissue (cerebral tissue oxygen saturation [tSo_2]) before, during, and after blood transfusion in a cohort of children presenting to hospital with severe anemia.

DESIGN, SETTING, AND PARTICIPANTS This was a prospective, observational cohort study conducted from February 2013 through May 2015 and analyzed in July 2015 at a university hospital pediatric acute care facility in Kampala, Uganda, of 128 children, ages 6 to 60 months who were enrolled in a larger clinical trial, with a presenting hemoglobin level of less than 5.0 g/dL and a blood lactate level greater than 5mM. Most children had either malaria or sickle cell disease.

EXPOSURES Red blood cell (RBC) transfusion given as 10 mL/kg over 120 minutes.

MAIN OUTCOMES AND MEASURES Clinical and laboratory characteristics of children with pretransfusion cerebral tSo_2 levels less than 65%, 65% to 75%, and greater than 75%. Change in cerebral tSo_2 as a result of transfusion.

RESULTS Of 128 children included in the study, oximetry results in 8 cases were excluded owing to motion artifacts; thus, 120 were included in this analysis. Cerebral tSo_2 values prior to transfusion ranged from 34% to 87% (median, 72%; interquartile range [IQR], 65%-76%). Eighty-one children (67%) demonstrated an initial cerebral tSo_2 level (≤75%) corresponding to an oxygen extraction ratio greater than 0.36. Patients with sickle cell disease (n = 17) and malaria (n = 15) contributed in nearly equal numbers to the subgroup with an initial cerebral tSo_2 (<65%). The level of consciousness, hemoglobin concentration, blood lactate level, and thigh muscle tSo_2 level were poor predictors of cerebral oxygen saturation. Following RBC transfusion, the median (IQR) cerebral tSo_2 level increased to 78% (73%-82%) (*P* < .001), but 21% of children failed to achieve a tSo_2 level greater than 75%.

CONCLUSIONS AND RELEVANCE Severe anemia in children is frequently associated with low cerebral oxygenation levels as measured by near-infrared spectroscopy. Hemoglobin level and lactate concentration did not predict low cerebral tSo_2 levels. Cerebral tSo_2 levels increase with RBC transfusion with different patterns of response. More studies are needed to evaluate the use of noninvasive cerebral tissue oximetry in the care of children with severe anemia.

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Worldwide, millions of children experience substantial morbidity and mortality from severe anemia each year.[1] The human brain has both a high resting oxygen extraction ratio and a high blood flow rate that combine to fulfill a continuous demand for oxygen. Children ages 2 to 6 years have higher cerebral blood flow rates and higher cerebral oxygen consumption rates (mL_{O_2}/gm/min) than adults.[2] The average cerebral metabolic rate in a child (5.25 milliliters of oxygen per gram per minute) represents more than 50% of total body oxygen consumption, whereas the average rate in an adult (3 mL_{O_2}/100 g/min) represents 20% of total body oxygen consumption.[3]

The higher oxygen demands of the pediatric brain make it more vulnerable to cerebral hypoxemia and injury in the setting of severe anemia. Silent cerebral ischemia and progressive neurocognitive deficits are well-recognized consequences of sickle cell disease (SCD),[4] and recent research from Uganda has demonstrated that severe anemia due to malaria is also associated with long-term neurocognitive impairment.[5] In sub-Saharan Africa, malaria, human immunodeficiency virus, nutritional deficiencies, and hemoglobin abnormalities cause severe pediatric anemia, commonly defined as a hemoglobin concentration of less than 5.0 g/dL (to convert hemoglobin to grams per liter, multiply by 10.0).[6] Currently, there is limited information on the extent to which severe anemia results in cerebral ischemia in children. Studying the effects of severe anemia on cerebral oxygenation represents one step toward a better understanding of the role that severe anemia may play in subsequent neurologic development and cognitive performance among children worldwide.

Noninvasive assessment of cerebral oxygenation is now available through several means. One approach uses devices that emit near-infrared (NIR) light at specific wavelengths absorbed by oxygenated and deoxygenated hemoglobin.[7] Optical probes (optodes), placed at a fixed distance from the light emitters, measure the reflectance by hemoglobin in tissue blood vessels, and report regional tissue oxygen saturation (tSo_2). Noninvasive measurements of cerebral tSo_2 have been shown to correlate with results measured by co-oximetry from samples obtained from the radial artery and jugular venous bulb of volunteers breathing different concentrations of oxygen.[8] Cerebral oximetry has been applied in diverse clinical settings, including cardiac surgery,[7,9] neonatal medicine,[7,10] and neurocritical care.[11] The technology has not been previously applied to children in sub-Saharan Africa with severe anemia.

Given the frequency and severity of pediatric anemia observed in sub-Saharan Africa[6,12-14] and the importance of the effective treatment of cerebral hypoxemia, we performed an observational study in Uganda designed to assess cerebral oxygenation before, during, and after red blood cell (RBC) transfusion in a cohort of children who presented to a pediatric urgent care facility with severe anemia associated with systemic lactic acidosis.

Methods

We studied tSo_2 as part of a larger randomized clinical trial of blood transfusion conducted at the pediatric acute care unit

Key Points

Question What are the results of cerebral oximetry obtained in children with severe anemia and lactic acidosis?

Findings In this cohort study of 120 Ugandan children with severe anemia, subnormal levels of cerebral oxygen saturation were commonly seen in children with malaria or sickle cell disease. In 21% of patients, cerebral oximetry did not normalize following a standard red blood cell transfusion.

Meaning Severe pediatric anemia is associated with abnormalities in cerebral oximetry, and given the worldwide prevalence of severe anemia in children, additional study of the extent and consequences of subnormal cerebral oxygenation in severe pediatric anemia seems warranted.

of Mulago Hospital in Kampala, Uganda. The design and primary outcome of that trial were reported previously.[15] Children, ages 6 to 60 months, who presented to hospital with a hemoglobin level of 5.0 g/dL or less and a blood lactate level of at least 5mM were screened for enrollment. We excluded children with severe acute malnutrition, known cardiac disease, or transfusion within the 48 hours prior to presentation. Written informed consent was obtained from the parent or guardian. Patients were enrolled between February 2013 and May 2015; they were not compensated for their participation. Patients were monitored for 24 hours after enrollment, and health status at 30 days was determined by telephone interview.[15] Data were analyzed in July 2015.

The study was approved by the School of Medicine Research Ethics Committee of Makerere University College of Health Sciences, the Uganda National Council for Science and Technology, and the Human Research Committee of the Massachusetts General Hospital. An independent oversight committee monitored enrollment and adverse events throughout the study. The study was registered at clinical trials.gov (NCT01586923).

Transfusions, Supplemental Oxygen, and Laboratory Assays

All patients received a transfusion of prestorage leuko-reduced CP2D-AS3 RBCs at a dose of 10 mL/kg by peripheral vein over 120 minutes using an electromechanical infusion pump. Some patients received small volumes of additional intravenous fluid (dextrose, antimalarial medications). Patients with an arterial oxygen saturation (Sao_2) of less than 95% (measured with finger oximetry) were given supplemental oxygen by nasal prongs. Hemoglobin and lactate concentrations were measured using point-of-care devices (Hemocue; Lactate-Pro LT-1710) validated in prior studies of severe anemia.[15] Hemoglobin and lactate concentrations were obtained just prior to transfusion (hour 0) and immediately at the completion of transfusion (hour 2).[15]

NIR tSo_2 Monitoring

Patients were monitored using a commercially available device (EQUANOX 7600, Nonin Medical Inc). All measurements were done over 120 minutes from the start to the completion of the RBC transfusion. Pediatric optodes, with an average light

Table. Clinical Features in All Patients and Features in 3 Subgroups According to Cerebral tSo$_2$ Values[a]

Characteristic	All Patients (n = 120)	Group A: tSo$_2$<65% (n = 32)	B: tSo$_2$ 65%-75% (n = 49)	C: tSo$_2$>75% (n = 39)	P Value
Cerebral tSo$_2$, median (IQR)	72 (65-76)	59 (49-62)	71 (69-73)	79 (76-81)	
Malaria, No. (%)	87 (73)	15 (47)	38 (77)	34 (87)	<.001
Sickle cell disease, No. (%)	25 (21)	17 (53)	6 (12)	2 (5)	<.001
Female:male	54:66	16:16	20:29	18:21	.71
Age, median (IQR), mo	27.5 (17-42)	27.5 (14-45)	30 (19-39)	27 (22-40)	.95
Mean arterial blood pressure, median (IQR), mm Hg	74 (65-80)	77 (69-81)	73 (68-80)	71 (63-81)	.25
Respiratory rate, median (IQR)	58 (50-63)	59 (50-68)	58 (50-62)	58 (49-62)	.68
Pulse rate, median (IQR)	162 (152-170)	153 (148-165)	166 (155-175)	162 (152-170)	.02
Stupor or coma, No. (%)	44 (37)	9 (28)	16 (32)	19 (49)	.15
Coma, No. (%)	11 (9)	1 (0.8)	4 (3)	6 (5)	.22
Hemoglobin, level, median (IQR), g/dL	3.2 (2.5-4.1)	2.8 (2.4-3.6)	3.1 (2.7-4.1)	3.4 (2.6-4.5)	.15
Systemic lactate, median (IQR), mM	9.3 (6.1-13.0)	9.9 (6.8-13.2)	8.7 (6.0-12.9)	9.4 (6.0-12.9)	.61
Sao$_2$, median, %	99	99	99	98	.71
Estimated cerebral venous oxygen saturation, median (IQR), %	61 (50-67)	42 (29-47)	61 (55-63)	70 (67-74)	NA
Estimated oxygen extraction ratio, median (IQR)	0.38 (0.30-0.48)	0.57 (0.52-0.68)	0.39 (0.34-0.44)	0.28 (0.22-0.31)	NA
Difference between thigh and brain tSo$_2$, median (IQR), %[b]	10.8 (8-19)	23 (20-33)	13 (9.7-16)	5.6 (3-9)	<.001
Supplemental, No. (%)					
Oxygen by nasal prongs	11 (9)	1 (3)	5 (10)	5 (13)	.40
Intravenous fluid[c]	49 (41)	13 (41)	17 (35)	19 (49)	.41
BNP, median (IQR), pg/mL	198 (45.5-696)	326 (97-866)	205 (54-676)	70 (20-390)	.13
Need for second transfusion, No. (%)	45 (37)	14 (44)	19 (39)	12 (31)	.52
Returned to good health at day 30, No. (%)[d]	87 (88)	22 (88)	33 (80)	32 (97)	.08
Died within 30 d, No. (%)[d]	8 (8)	2 (8)	5 (12)	1 (3)	.41

Abbreviations: BNP, B-type natriuretic peptide, measurements in 30, 38, and 27 patients in groups A, B, and C, respectively; IQR, interquartile range; NA, comparison not applicable based on definition of groups A, B, and C; Sao$_2$, arterial oxygen saturation; tSo$_2$, tissue oxygen saturation.

SI conversion: To convert hemoglobin to grams per liter, multiply by 10.0.

[a] All data were obtained prior to transfusion.

[b] Simultaneous cerebral and thigh measurements in 18, 26, and 28 patients in groups A, B, and C, respectively.

[c] Median (IQR) volume given to those receiving fluid = 50 mL (40-60 mL).

[d] Data apply to 25, 41, and 33 patients in groups A, B, and C, respectively.

penetrance of 12.5 mm, were placed on the left side of the forehead above the eyebrow according to the manufacturer's directions. Readings were recorded electronically every 4 seconds, and the data transferred to a digital database for analysis. In a subset of 72 children, we placed a second optode on the left thigh to obtain simultaneous readings from thigh muscle. The device uses NIR light emitters at 4 different wavelengths to measure the reflectance of oxygenated and deoxygenated hemoglobin. Data are combined to generate a single read-out value that estimates the percentage of tSo$_2$. The reported result assumes the hemoglobin saturation in the blood of cerebral tissue is approximated by

$$tSo_2 = 0.3(Sao_2) + 0.7(Oxygen\ Saturation).$$

In healthy individuals, the mean (SD) cerebral tSo$_2$ using 4-wavelength NIR spectroscopy is reported as 76% (4.8%).[16,17]

For each patient, a graph of tSo$_2$ over time was prepared by plotting, at 5-minute intervals, the average reading for 1 minute (average of 15 readings). The graph was prepared from the device readings by an individual not involved in the care of the patient and without access to other clinical data. Using the starting value as the baseline, software (Prism 6; Graphpad Inc) was used to compute the net area under the curve (AUC) of tSo$_2$ as a function of time for 120 minutes during transfusion. The net AUC represents the overall change in oxygen saturation in response to transfusion. Arterial oxygen saturation was directly measured by finger pulse oximetry. The estimated venous oxygen saturation was directly calculated from the recorded tSo$_2$ and the measured Sao$_2$ using the formula above. The estimated local tissue oxygen extraction ratio was then calculated from the measured Sao$_2$ and estimated venous oxygen saturation.

Statistical Analysis

Continuous variables are presented as median and interquartile ranges (IQRs) and compared using the Mann-Whitney test (2 variables) or the Kruskal-Wallis test (3 variables).

The relationship between hemoglobin level and initial tSo$_2$ level, between lactate level and initial tSo$_2$ level, and between initial cerebral tSo$_2$ level and thigh tSo$_2$ level were examined by linear correlation using GraphPad Prism 6. The correlation coefficient r^2 was determined by the method of least squares. The area under the oxygen saturation curve during transfusion was plotted as a function of the initial tSo$_2$, fitted to a 1-phase exponential curve using GraphPad Prism 6, and the goodness of fit (R^2) determined by the method of least

Figure 1. Distribution of Cerebral Tissue Oxygen Saturation (tSo$_2$) Values Before and After Red Blood Cell Transfusion in 120 Children Presenting With Severe Anemia and Lactic Acidosis
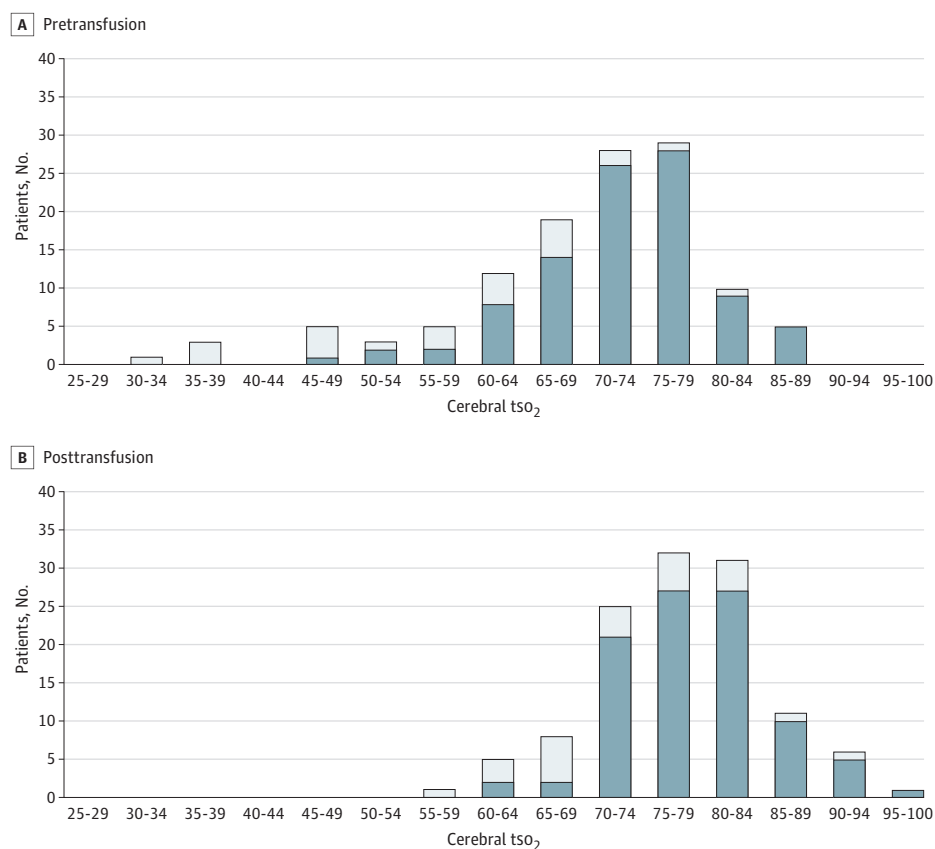
A, Pretransfusion. B, Posttransfusion. The white sections of the bars indicate patients with sickle cell anemia. The mean (SD) normal cerebral tSo$_2$ is 76% (4.8%).[16,17]

squares. A paired test (Wilcoxon signed rank test) was used to compare oxygen saturation before vs after transfusion within the same individual. Categorical variables were compared using the Fisher exact test. The threshold for significance was $P < .05$. All comparisons were 2-sided. No corrections were made for multiple comparisons.
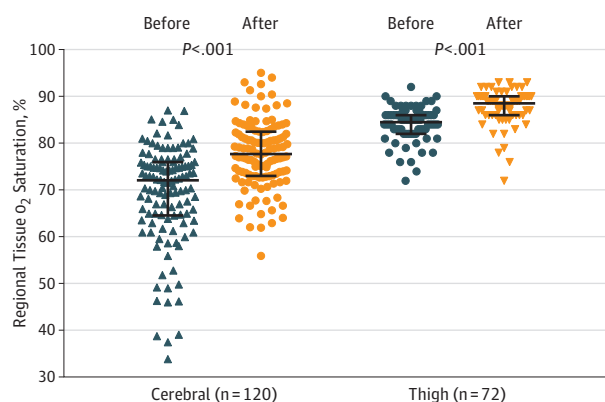
Results

Noninvasive cerebral oximetry was performed in 128 patients who presented to a pediatric acute care unit in Kampala, Uganda, and who were enrolled in a larger clinical trial of blood transfusion.[15] In 8 cases, the readings were considered unreliable owing to motion artifacts. The remaining 120 cases form the basis for this report.

Baseline Clinical Features

At presentation to hospital, the patients were severely anemic with a median (IQR) hemoglobin level of 3.2 g/dL (2.5-4.1 g/dL) and a median (IQR) blood lactate level of 9.3mM (6.1mM-13.0mM) (Table). The patients had tachycardia and tachypnea but were not hypotensive. Stupor or coma was initially present in 37% of children. A minority of children (9%) who presented with an Sao$_2$ level of less than 95% were given supplemental oxygen by nasal prongs and achieved a saturation level greater than 95%. Patients were not in shock and not given bolus intravenous fluids. Most children (73%) had malaria, and 21% had SCD. Initial cerebral tSo$_2$ values ranged from 34% to 87% with a median (IQR) value of 72% (65%-76%). These values correspond to a median (IQR) extraction ratio of 0.38 (0.30-0.48). Eighty-one of 120 children (67%) presented with cerebral tSo$_2$ of 75% or less, corresponding to an oxygen extraction ratio greater than 0.36. The distributions of cerebral tSo$_2$ values before and after RBC transfusion are shown in Figure 1.

We categorized the patients into 3 subgroups based on their pretransfusion cerebral tSo$_2$ values: tSo$_2$ level of less than 65% (n = 32), tSo$_2$ level of 65% to 75% (n = 49), and tSo$_2$ level greater than 75% (n = 39). Clinical features for each group are shown in the Table. The subgroup with cerebral tSo$_2$ level of less than 65% (32 patients) consisted of equal numbers of patients with malaria and SCD. Sickle cell disease was present in 17 of 32 (53%) of those with an initial cerebral tSo$_2$ level of less than 65%, but only 2 of 39 (5%) of those with an initial cerebral tSo$_2$ level greater than 75% ($P < .001$). The median (IQR) initial tSo$_2$ level among 25 patients with SCD was 60% (49%-66%), which was significantly lower than the median value among 95 patients without SCD, 74% (69%-77%) ($P < .001$). The lower cerebral tSo$_2$ level among

Figure 2. Regional Tissue Oxygen Saturation (tSo$_2$) Levels Before and After RBC Transfusion
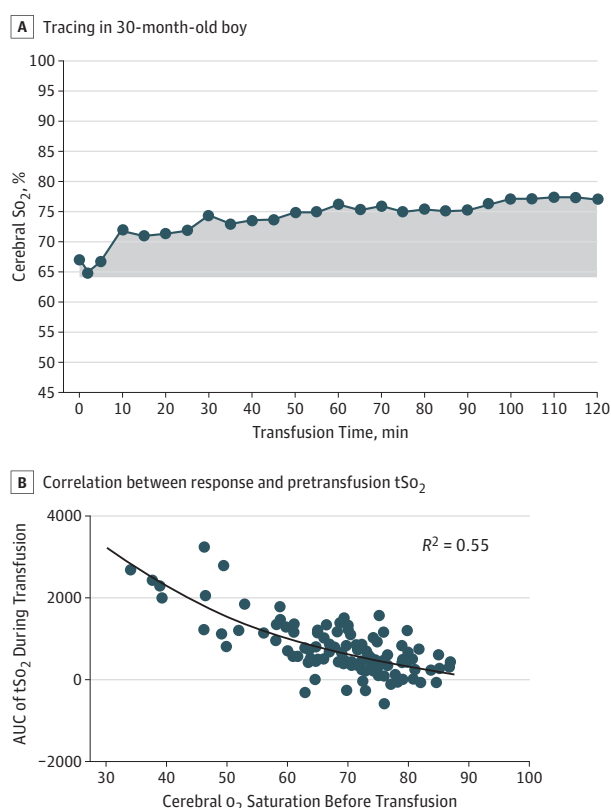

A, Levels from the brain (n = 120). B, Levels from the thigh (n = 72). The horizontal bars are the median values, and the error bars are the interquartile ranges. In both tissues, there was a significant increase in tSo$_2$ as a result of transfusion.

Figure 3. Cerebral Tissue Oxygen Saturation (tSo$_2$) in Response to Red Blood Cell Transfusion

A Tracing in 30-month-old boy

B Correlation between response and pretransfusion tSo$_2$

A, An individual tracing in a 30-month-old boy with partially treated malaria who presented to the hospital with a hemoglobin concentration of 3.2 g/dL and lactate level of 5.9mM. The child was alert, with a blood pressure 104/58 mm Hg, pulse of 163 beats/min, and respiratory rate of 62 breaths/min. The average cerebral tSo$_2$ values are shown every 5 minutes during transfusion with 10 mL/kg of red blood cells. The region shaded in gray is the area under the curve (AUC) using the initial value as the baseline. B, Correlation between response to transfusion, measured as AUC, and the pretransfusion cerebral tSo$_2$ in the study group of 120 patients.

patients with SCD occurred despite the fact that their hemoglobin concentration and their SaO$_2$ level were not significantly different from the patients without SCD: hemoglobin values, 2.9 g/dL (2.3-3.6 g/dL) for patients with SCD vs 3.2 g/dL (2.6-4.3 g/dL) for patients without SCD (P = .11); SaO$_2$ level, 98% (94%-99%) for patients with SCD vs 99% (96%-100%) for patients without SCD (P = .14). The median (IQR) cerebral oxygen extraction ratio for patients with SCD was 0.53 (0.46-0.72) compared with 0.34 (0.29-0.43) for patients without SCD (P < .001).

Predicting Cerebral tSo$_2$

As shown in the Table, the level of consciousness was not associated with low cerebral tSo$_2$ level. All patients had an initial hemoglobin measurement of less than 5.0 g/dL. While the lowest cerebral tSo$_2$ levels were observed in patients with hemoglobin values of less than 4.0 g/dL, there was very poor correlation (r^2 = 0.08) between hemoglobin concentration and cerebral tSo$_2$ level (see eFigure 1 in the Supplement). All patients had an initial blood lactate level greater than 45.0 mg/dL (median, 83.8 mg/dL) with values ranging as high as 186.5 mg/dL. However, systemic lactate concentrations also did not correlate with cerebral tSo$_2$ level (r^2 = 0.02) (see eFigure 2 in the Supplement).

In 72 patients, regional tissue oxygen saturation was simultaneously measured in the left frontal brain and left thigh every 4 seconds for 120 minutes during transfusion. In 86% of cases, thigh tSo$_2$ level was higher than cerebral tSo$_2$ level throughout the transfusion. Prior to transfusion, the median (IQR) difference in tSo$_2$ between the 2 tissues was 10.8% (8.0%-19.0%). This difference was maintained following transfusion, 9.3% (6.7%-14.0%) (Figure 2). A low cerebral tSo$_2$ level was not reflected by a corresponding low thigh tSo$_2$ level. Rather, patients with low cerebral tSo$_2$ level showed a larger difference between thigh and cerebral readings (Table). Thigh tSo$_2$ level did not correlate with cerebral tSo$_2$ level (r^2 = 0.12) and could not be used as a surrogate measurement for the cerebral saturation (see eFigure 3 in the Supplement).

Response to RBC Transfusion

All 120 patients received transfusion of RBCs as 10 mL/kg over 120 minutes. Transfusion reproducibly increased cerebral tSo$_2$. The median (IQR) cerebral tSo$_2$ level before transfusion was 72% (65%-76%) and rose to 78% (73%-82%) after transfusion (P < .001) (Figure 2). The overall time-integrated increase in cerebral oxygenation was measured as the AUC of the plot of cerebral tSo$_2$ level over time during transfusion (Figure 3). A higher AUC reflects a greater overall increase in cerebral oxygen saturation. The median (IQR) AUC during transfusion was 553 (319-1052). As shown in Figure 3, the magnitude of cerebral tSo$_2$ response to transfusion, as measured by the AUC, was not "fixed" even though the dose of hemoglobin was the same for all patients (10 mL/kg). Rather, patients presenting with lower cerebral tSo$_2$ obtained greater benefit (higher AUC) from transfusion.

The median (IQR) hemoglobin concentration rose from 3.2 g/dL (2.5-4.1 g/dL) just prior to transfusion to 6.1 g/dL (5.2-7.2 g/dL) immediately after transfusion, resulting in a doubling of the oxygen content of blood delivered to the

Figure 4. Representative Examples of the Most Common Patterns of Cerebral Tissue Oxygen Saturation (tSo$_2$) Response to Transfusion
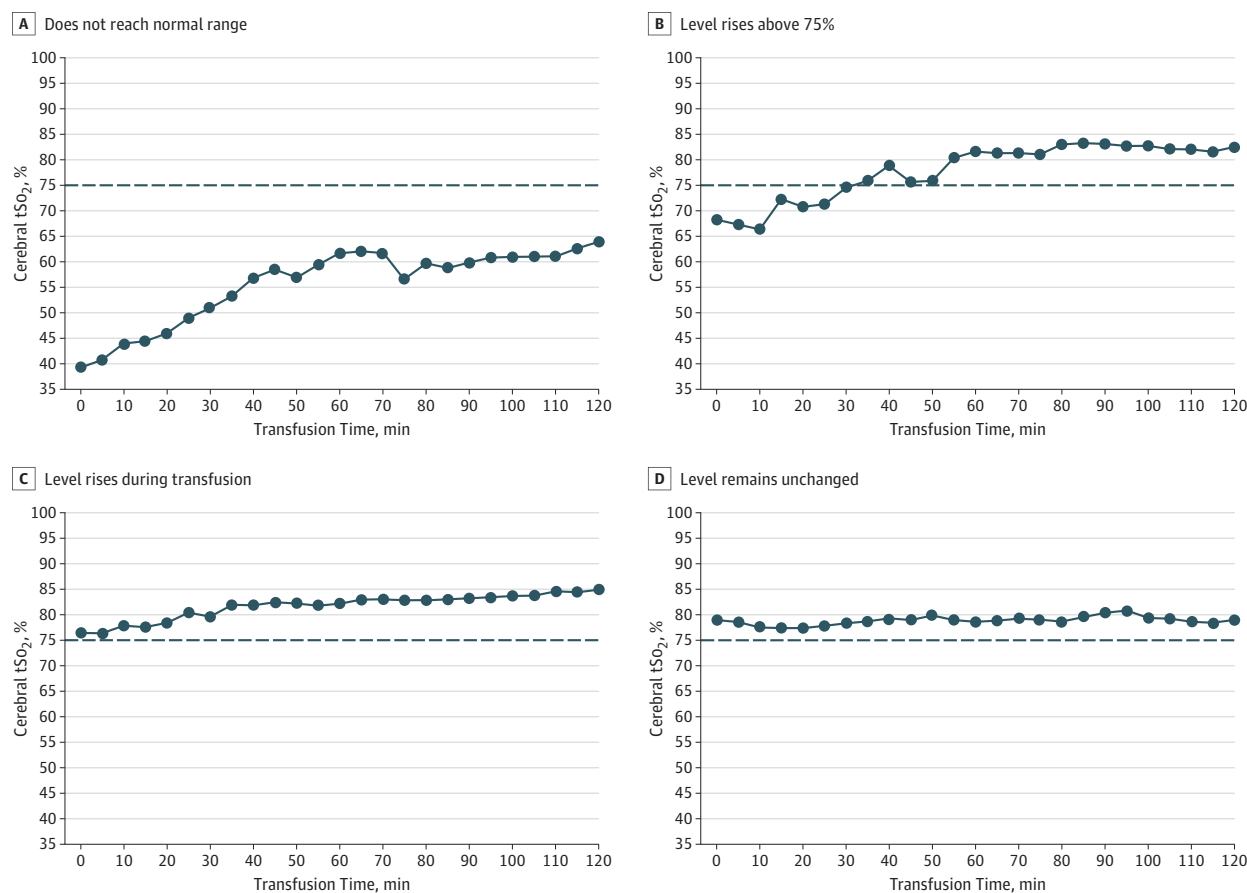
A, Cerebral tSo$_2$ begins at a very low value, improves with transfusion, but does not reach the normal range. B, Cerebral tSo$_2$ rises above 75% during the transfusion. C, Cerebral tSo$_2$ begins above 75% and rises during transfusion. D, Cerebral tSo$_2$ remains relatively unchanged during transfusion. The horizontal dashed lines correspond to an oxygen extraction ratio of approximately 36%.

brain. Patients showed different patterns of cerebral tSo$_2$ in response to transfusion. Representative examples of the 4 most common patterns are shown in **Figure 4**. Additional examples illustrating less common cerebral oximetry responses are shown in eFigures 4 to 9 in the Supplement. The pattern shown in Figure 4A occurred in 21%, the pattern in Figure 4B in 33%, the pattern in Figure 4C in 16%, and the pattern in Figure 4D in 25% of patients. For most patients, cerebral tSo$_2$ levels rose (patterns A, B, and C in Figure 4), providing direct evidence of decreasing oxygen extraction in association with increasing hemoglobin. However, in 21% of patients (pattern A in Figure 4) cerebral tSo$_2$ level at the end of transfusion did not reach normal values, indicating ongoing high oxygen extraction ratios in the cerebral circulation at the end of transfusion.

Discussion

We present the first case series, to our knowledge, of cerebral oxygen measurements in children presenting with hemoglobin levels of less than 5.0 g/dL. The data from patients in this study are informative because the observed cerebral oximetry values were the direct consequence of severe anemia and were not confounded by hemorrhage, hypotension, sepsis, cardiac disease, trauma, or uncorrectable hypoxia. Because the brain of a child has an especially high resting blood flow and high metabolic demand for oxygen, regional cerebral oxygen measurements may be especially valuable in the assessment of the effects of severe anemia.

Based on previous publications,[16-18] we categorized patients into those whose initial tSo$_2$ levels were 65% or less, 65% to 75%, and greater than 75%. We found that cerebral tSo$_2$ levels of 75% or less were common, occurring in two-thirds of individuals, thus emphasizing the high proportion of individuals at risk for potential morbidity. Among children with SCD, values of 65% or less were significantly more common, a finding consistent with 2 prior studies[16,19] in less anemic children with SCD. Patients with SCD are known to be at risk for silent cerebral infarction,[20] and a program of regular transfusion has been shown to decrease the rate of recurrent cerebral infarcts.[21] Of note, we observed an equal number of cases with cerebral tSo$_2$ levels of less than 65% among children with malaria. The observed differences in cerebral tSo$_2$ levels at similar levels of

hemoglobin concentration suggest that some patients with SCD or malaria have additional impairment of cerebral tissue oxygenation, perhaps as a result of cytoadhesion, reduced nitric oxide bioavailability, or microvascular occlusion. Each year, an estimated 300 000 children are born with SCD. Severe malaria anemia, which is much more common than SCD, may affect as many as 5 million children annually and recently has also been associated with impaired neurocognitive development.[5] The exact relationship between the observed cerebral oximetry measurements and subsequent impaired cognition is unknown, but our findings suggest that assessment of cerebral tSO_2 level may be valuable in future studies of pediatric severe anemia.

We found that cerebral tSO_2 levels were not predicted by level of consciousness. In addition, hemoglobin concentration and systemic blood lactate levels, 2 tests commonly used to assess the need for blood transfusion, did not correlate well with cerebral tSO_2, suggesting that these standard laboratory measures might not adequately assess regional cerebral oxygenation.[19,22,23] Although many reports have monitored patients using a NIR spectroscopy probe placed on a limb,[7] we found that thigh tSO_2 measurements also did not correlate with cerebral tSO_2, emphasizing the regional nature of oxygen supply vs demand in specific tissues.

The effect of transfusion on cerebral tSO_2 levels has been documented in neonates.[7,10,23-26] Previous reports have also used NIR spectroscopy to guide the decision to transfuse RBCs during surgery or in other critical care settings.[7,9-11] While many studies concluded that NIR spectroscopy improved transfusion management, other studies, conducted in less severely anemic patients, failed to find value in the technology.[27,28] Although transfusion of stored RBCs with reduced 2,3-diphosphoglycerate and higher oxygen affinity might be expected to increase venous SO_2 level and thus the calculated tSO_2 level independent of improved tissue oxygenation, we previously reported in a randomized clinical trial that RBC storage duration did not influence the cerebral tSO_2 response to transfusion as measured by NIR spectroscopy.[15] Our patients showed rapid improvement of cerebral tSO_2 level in response to RBC transfusion. The extent of response was highest in those with the lowest initial cerebral tSO_2 levels. A similar observation was made after transfusion of premature neonates.[26] Different patterns of response to transfusion were observed, including an important subgroup of patients (21%) who did not achieve a normal cerebral tSO_2 level following the dose of RBCs recommended by World Health Organization guidelines. Their response highlights the idea that a weight-based transfusion dose or a single target hemoglobin level for completion of transfu-

sion might not be sufficient for all patients.[29-31] Future studies may identify if noninvasive cerebral monitoring can objectively identify those patients with severe anemia most likely to benefit from additional RBC transfusion.

Our study was observational and has several weaknesses. We did not measure cardiac output and so could not formally calculate oxygen delivery (milliliters of oxygen per kilogram per minute). However, determination of global oxygen delivery may be misleading in some settings because it ignores the regional nature of oxygen supply vs demand in specific organ beds. Regional tissue-specific oxygenation rather than total oxygen delivery is, in fact, a major proposed advantage of NIR spectroscopy. While the method obtains information from a representative area of the brain, it does not measure global brain ischemia. The calculations used by the manufacturer to estimate cerebral tSO_2 level are based on data obtained from individuals who were not as anemic as the patients in our study. Values for NIR spectroscopy are also known to vary between individuals, making group comparisons difficult. For these reasons, the pretransfusion vs posttransfusion changes we recorded for each patient are likely to be more reliable measures. We did not perform electroencephalograms or other forms of central nervous system monitoring to refine the assessment of cerebral hypoxemia, nor could we obtain long-term neurocognitive follow-up on patients. Although this was the largest study, to our knowledge, of cerebral NIR spectroscopy in children with severe anemia, our sample size was not sufficient to examine independently multiple categories of patient response to transfusion. Enrollment was restricted to patients with very severe anemia associated with lactic acidosis, and our findings may not apply to children with less severe forms of anemia.

Conclusions

We present results of cerebral oximetry in a large cohort of children with severe anemia associated with lactic acidosis. Low values for cerebral tSO_2 level were common and present in children with SCD and malaria. Level of consciousness and traditional markers of adequate tissue oxygenation, such as hemoglobin concentration and lactate levels, were poor predictors of cerebral tSO_2 level. Transfusion measurably increased brain tSO_2 with different patterns of response. More research is needed to understand how cerebral oximetry can be used to optimize blood transfusion management in children with severe anemia and to better understand the effects of cerebral hypoxemia on childhood health and development.

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