Published in final edited form as:

Pediatr Blood Cancer. 2009 May ; 52(5): 609–615. doi:10.1002/pbc.21738.

A PILOT STUDY OF HYDROXYUREA TO PREVENT CHRONIC ORGAN DAMAGE IN YOUNG CHILDREN WITH SICKLE CELL ANEMIA

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Abstract

Background—Hydroxyurea improves laboratory parameters and prevents acute clinical complications of sickle cell anemia (SCA) in children and adults, but its effects on organ function remain incompletely defined.

Methods—To assess the safety and efficacy of hydroxyurea in young children with SCA and to prospectively assess kidney and brain function, 14 young children (mean age 35 months) received hydroxyurea at a mean maximum tolerated dose (MTD) of 28 mg/kg/day.

Results—After a mean of 25 months, expected laboratory effects included significant increases in hemoglobin, MCV and %HbF along with significant decreases in reticulocytes, absolute neutrophil count, and bilirubin. There was no significant increase in glomerular filtration rate by DTPA clearance or Schwartz estimate. Mean transcranial Doppler (TCD) velocity changes were −25.6 cm/sec ($p<0.01$) and −26.8 cm/sec ($p<0.05$) in the right and left MCA vessels, respectively. At study exit, no child had conditional or abnormal TCD values, and none developed brain ischemic lesions or vasculopathy progression by MRI/MRA. Growth and neurocognitive scores were preserved and Impact-on-Family scores improved.

Conclusions—These pilot data indicate hydroxyurea at MTD is well-tolerated by both children and families, and may prevent chronic organ damage in young children with SCA.

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Keywords

sickle cell anemia; hydroxyurea; children

INTRODUCTION

Hydroxyurea can increase fetal hemoglobin (HbF) levels and ameliorate clinical severity in patients with sickle cell anemia (SCA). A randomized, double-masked, placebo-controlled trial in severely affected adults with SCA found that hydroxyurea significantly reduced painful vaso-occlusive events (VOE), acute chest syndrome (ACS), hospitalizations, and red cell transfusions [1]. Subsequently, a phase I/II trial of hydroxyurea in children with SCA (HUG-KIDS) age 5– 15 years demonstrated similar safety and hematological efficacy as in adults [2]. Clinical efficacy using open-label hydroxyurea has been reported in small series of children [3–5]. More recently, the prospective HUSOFT Phase I/II pilot study determined the feasibility and safety of hydroxyurea therapy for very young children with SCA between the age of 6– 24 months; in the short term [6] and with extended follow-up [7]; hydroxyurea was well tolerated with no negative effects on growth or development [6].

Although hydroxyurea has an established track record for improving laboratory parameters and reducing acute clinical complications, its role in preventing organ damage in SCA is less well defined. Organ damage in young children with SCA includes early splenic damage with parenchymal infarction and decreased immunological function, renal dysfunction with glomerular hyperfiltration and loss of concentrating ability, and substantial cerebrovascular and neurocognitive defects. In HUSOFT, the incidence of splenic dysfunction in hydroxyurea-treated children was less than predicted for age, suggesting some degree of organ protection. In retrospective analyses, hydroxyurea in children with SCA may have beneficial effects for the spleen [8], brain [9], kidney [10], and lung [11]. To date, however, no prospective study using hydroxyurea to preserve organ function in SCA has been reported.

To investigate organ function in patients with SCA taking hydroxyurea, we designed a prospective pilot study called Toddler hydroxyurea group (Toddler HUG, NCT00519701). The primary objectives were to assess the safety and efficacy of hydroxyurea in young children with SCA (age 18 months5 years) and to determine changes in glomerular filtration rate (GFR), transcranial Doppler (TCD) velocities and brain ischemia and vasculopathy after 2 years of hydroxyurea. Secondary objectives included evaluation of neurocognitive outcomes and health-related quality of life (HRQL).

METHODS

Enrollment and Screening

Children with SCA (HbSS or HbSβ^o thalassemia) between 18 months and 5 years receiving medical care at Duke University were eligible to participate in this prospective pilot study. After parents signed written consent, children underwent screening evaluations for organ function including quantitative GFR measurement by radionuclide diethylenetriamine

pentaacetic acid (DTPA) clearance and GFR estimate by the Schwartz formula based on serum creatinine [12,13], TCD time-averaged maximal mean middle cerebral artery (MCA) velocity measurement, and brain MRI/MRA [14,15]. Laboratory evaluation included complete blood counts, %HbF, and serum chemistries. Children underwent neurocognitive testing using the McCarthy Scales of Children's Abilities (MSCA) for children age 2½ to 8½ years, which provides a standardized assessment of verbal; motor; memory; quantitative; general cognitive (CGI); and perceptual-performance. The Bayley Scales of Infant Development-Version II was used for younger children. The Mental Developmental Index (MDI) that correlates with the CGI and Psychomotor Index (PDI) were obtained from the Bayley Scales. HRQL assessments included the Pediatric Health Related Quality of Life Measure (PedsQL™ Parent Report for Toddlers ages 2–4 Version 4.0) [16] and the Impact-on-Family (IOF) Scale [17].

Hydroxyurea dosing. Hydroxyurea treatment was initiated at 20 mg/kg/day using a liquid preparation [6], and escalated by 5 mg/kg/day every 8 weeks to a maximum tolerated dose (MTD) or 30 mg/kg/day [18]. The hydroxyurea solution was dispensed monthly as described [19].

Study tests and monitoring

Children were monitored for hematological responses and hematological, renal and hepatic toxicities. Subjects who completed 2 years of therapy had TCD examination, DTPA GFR measurements, and brain MRI/MRA at study exit. HRQL ratings were provided at baseline, mid-point and study exit. Complete neurocognitive testing was performed at baseline and study exit.

Statistical analyses

This was designed as a pilot study with a convenience sample preceding the opening of NHLBI-sponsored Phase III BABY HUG clinical trial (NCT00006400). Power calculations were not done *a priori* as we planned to use the results as hypothesis generating. Descriptive statistics were used to determine means and standard deviations. The Student's paired t test was used to test for differences between baseline and exit hematological, TCD and GFR variables. Pearson correlation coefficients were calculated between DTPA GFR and Schwartz estimate at baseline and exit. These data were analyzed with R programming language with no adjustment for multiple comparisons [20]. Baseline and exit cognitive standard scores were compared using a mixed model analysis to test for differences between baseline and exit. Baseline, midpoint and exit HRQL and IOF were compared using a mixed model analysis to test for a linear trend. Mixed models were performed using SAS software (SAS Institute, Cary, NC) [21]. All statistical tests are 2 tailed and an alpha level of .05 was used for significance.

RESULTS

Baseline characteristics

Fourteen subjects enrolled and participated for ≥80 weeks (Table I). Eleven were male; all 14 had HbSS and 1 had 2-gene deletion alpha thalassemia trait. The average age at

enrollment was 35 months (range 21–53 months). One child enrolled but stopped hydroxyurea after eight months from lack of parental resources; this child was excluded from analysis. No child in this study participated in another hydroxyurea clinical trial. The Toddler HUG study was closed to accrual upon opening of BABY HUG to promote enrollment into that randomized trial.

Prior to study enrollment, 12 of 14 subjects had significant acute clinical events including dactylitis, painful VOE, bacteremia, ACS and acute anemia as defined by the Cooperative Study of Sickle Cell Disease (CSSCD) [22]. Two children underwent splenectomy for acute splenic sequestration before enrollment. Two children with subacute splenic sequestration did not undergo splenectomy; one developed acute splenic sequestration immediately prior to enrollment and received transfusions for two months during hydroxyurea initiation but did not undergo splenectomy. Two children experienced only fever before enrollment.

Hematological efficacy

Baseline hematological parameters were similar to reported values for infants followed in CSSCD (e.g., mean hemoglobin 8.0 g/dL, range 6.4–10.6 g/dL) [23]. All 14 children completed hydroxyurea dose escalation and reached an average MTD of 28mg/kg/day (range 20–34 mg/kg/day). One child received 34 mg/kg/day with persistent reticulocytosis and minimal myelosuppression; the MTD for all others was ≤30 mg/kg/day. The average duration of hydroxyurea therapy was 25 months (range 18.4–32.9 months). One subject left the study at week 80 due to parental request with a difficult social situation. Another subject was removed from study at week 89 after developing recurrent thrombocytopenia and hypersplenism. Hematological changes between baseline and exit included significant increases in hemoglobin concentration, mean corpuscular volume (MCV), and %HbF and significant decreases in reticulocyte count, absolute neutrophil count (ANC), and serum bilirubin (Table II).

Renal function

Eleven children had DTPA GFR assessed at entry and exit. The average GFR at entry was 139.2 ± 19.5 mL/min/1.73 m^2 and elevated above 150 mL/min/1.73 m^2 in 5 children. After 2 years, the average GFR value did not rise as expected in this age range (mean change 5.1 mL/min/1.73 m^2; 95% CI = −4.39 to 14.6; p=0.26) (Figure 1). Two children with GFR measurements over 150 mL/min/1.73 m^2 at entry had measurements <150 mL/min/1.73 m^2 at study exit. At entry, the correlation between DTPA GFR quantitation and Schwartz estimate was 0.53 (95% CI = −0.03 to 0.83; p=0.06) (Figure 2). At study exit, the correlation between DTPA and Schwartz estimate was 0.68 (95% CI = 0.13 to 0.91; p<0.05).

TCD and MRI/MRA results

TCD and brain MRI/MRA were performed at study entry and exit for 12 and 11 children, respectively. Three children had conditional TCD velocities at study entry, with highest time-averaged maximal mean velocity values of 171, 177, and 177 cm/sec respectively; no child had abnormal baseline TCD velocities. At study exit, average TCD values significantly decreased with an average reduction of 25.6 ± 27.6 cm/sec in the right MCA (95% CI = 8.1 to 43.1; p<0.01) and 26.8 ± 32.6 cm/sec in the left MCA (95% CI = 6.1 to 47.6; p<0.05)

(Figure 3). The 3 children with conditional TCD velocities had normal exit values (96, 114, and 111 cm/sec, respectively). One child had mild small vessel ischemic changes on entry brain MRI, which were stable on exit MRI. Two children had mild to moderate A1 stenosis bilaterally on initial MRA, which were stable or improved at study exit (data not shown).

Neurocognitive testing

Complete neurocognitive testing was performed for 12 children at baseline and 9 at exit; mean functioning was within the normal range. Between entry and exit, mean standard scores increased by 2.0 points, not statistically significant (95% CI = −21.4 to 25.5; p=0.70) (Table III).

Growth data

Changes in growth on treatment are depicted in Figure 4. At study exit, children had maintained growth parameters or even crossed percentiles upward.

HRQL testing

HRQL ratings were provided by caregiver proxy report for 13 children at baseline, 11 at mid-point, and 8 children at study exit. Caregiver-reported HRQL was below the average expected for healthy individuals (Table III). Mixed model analysis indicated no significant changes over time for global HRQL between study time points (slope= 1.0; 95% CI = −3.9 to 5.9; p=0.67). However, IOF scores significantly decreased from baseline to exit (slope= −5.3; 95% CI = −8.2 to −2.5; p=0.001), indicating parental perception of less impact of the child's disease on family functioning over time.

Toxicity

23 instances of hematological toxicity occurred among 9 children: 11 neutropenia, 6 anemia, 4 thrombocytopenia (all in one child) and 2 combined cytopenias. Typically, hydroxyurea was held for one week and the toxicity resolved; minor dose adjustments were made for 11 toxicities. The longest hydroxyurea hold was 14 weeks with myelosuppression and then splenic sequestration. No significant infections from myelosuppression or bleeding with thrombocytopenia occurred. No child experienced hepatic or renal toxicity, and there was no evidence of blood dyscrasias based on peripheral blood counts.

Clinical events

Over the 2-year treatment period, three children required a single transfusion each for ACS, hypoplastic anemia, and splenic sequestration. One episode of *Moraxella catarrhalis* bacteremia occurred unrelated to myelosuppression, which responded to antibiotics. Only two episodes of ACS occurred, including one mild episode not requiring transfusion. There were two hospitalizations for painful VOE.

Hydroxyurea and splenic sequestration

One child was removed from study at week 89 after developing recurrent thrombocytopenia and hypersplenism. A second child had acute splenic sequestration but continued hydroxyurea without recurrence, and a third with previous acute splenic sequestration did

not recur during the study. Two children with prior subacute splenic sequestration also did not have recurrent splenomegaly.

DISCUSSION

Toddler HUG is the first prospective study, designed specifically to assess chronic organ damage in young children with SCA taking hydroxyurea. In the majority of these 14 toddlers, quantitative assessments of brain and kidney function could be obtained. Our study provides pilot data suggesting that hydroxyurea may prevent chronic organ damage in young children with SCA.

We previously showed that hydroxyurea has beneficial effects on the brain: hydroxyurea at MTD can help prevent secondary (recurrent) stroke [24,25] and also can lower elevated TCD velocities [15] so may help prevent primary stroke. In retrospective analysis, children on hydroxyurea developed fewer cerebral ischemic events than expected for age [7,8]. In the current Toddler HUG study, children had decreased TCD velocities after two years of hydroxyurea therapy. Since only three children had conditional TCD velocities at study entry, the overall risk of conversion to abnormal TCD was low [26]; however, no child had new radiologic CNS changes at an age when asymptomatic MRI/MRA abnormalities develop [27,28]. Randomized studies must be conducted to test whether hydroxyurea can prevent primary or silent stroke. The ongoing Phase III SWiTCH clinical trial (NCT00122980) will test the hypothesis that hydroxyurea prevents secondary stroke.

In CSSCD, children with silent infarcts or overt stroke performed significantly worse on neuropsychological testing than unaffected children [29]. Thompson *et al.* showed that even without demonstrable clinical or neurological events, young children with SCA are at significant risk for poor neurocognitive outcome [30]. In Toddler HUG, baseline neurocognitive data were normal with preservation of neurocognitive functioning. This is encouraging since children with SCA and normal MRI/MRA often develop global and/or specific neuropsychological functioning deficits compared to siblings or healthy subjects [27,29,31–33]. Further study is needed to test whether hydroxyurea prevents the observed decline in neurocognitive functioning described in CSSCD [29].

Renal damage in SCA begins in early childhood with loss of urine concentrating ability and glomerular hyperfiltration [34]. The glomerular filtration rate is typically normal (100 ± 20 mL/min/1.73m^2) early in life, but increases to >150 mL/min/1.73m^2 by age 6 years and >200 mL/min/1.73m^2 by age 10 years [2,35]. Increased GFR is a marker of hyperfiltration, which is associated with glomerular hypertrophy and glomerulosclerosis. We previously reported a potential effect of hydroxyurea and enalapril on sickle nephropathy l [10], but no studies have prospectively investigated the effects of hydroxyurea on renal function in SCA. There was limited correlation between DTPA GFR and Schwartz estimate at study entry and only slightly better correlation at study exit. We recommend that quantitative DTPA GFR be the measure of renal function in patients with SCA. In Toddler HUG, no increases in DTPA GFR were observed during a time when children with SCA typically develop glomerular hyperfiltration [35].

Hydroxyurea may have salutary effects on growth in children with SCA. Among adults in the Multicenter Study of Hydroxyurea, there was improved weight gain and exercise tolerance compared to adult controls [36]. In HUG-KIDS and HUSOFT extension children had stable to improved growth parameters [7,37]. Children in Toddler HUG had stable or accelerated growth velocity for weight and height. We hypothesize that improved growth is related to decreased hemolysis, decreased energy expenditure, and improved oral intake, all of which should promote normal growth.

Quality of life is an important clinical outcome in SCA since both adults and children have reduced HRQL compared to national norms [38–40]. We did not observe improved HRQL over our two-year treatment period, but HRQL did not decrease despite the increased clinic visits and daily administration of hydroxyurea. Importantly, we observed a significant improvement on disease impact on the family. This result may be related to better coping skills over time or increased contact and support from clinical staff. In addition, since children on hydroxyurea had few clinical events, we hypothesize that decreased IOF scores are primarily related to improved clinical status. We anticipate that this improvement could lead to improved HRQL and even improved cognitive functioning over time.

As a small, single institution, non-randomized study, the results cannot be generalized. For unclear reasons the majority of subjects were male but most were adherent with study visits. Unfortunately, adherence with study-related tests was problematic, contributing to missing data; especially neurocognitive testing. The missing data and small sample size limit the power of the study to detect changes in organ function and HRQL over time.

In conclusion, this prospective Toddler HUG pilot study using open-label hydroxyurea therapy confirms the feasibility of organ function testing in very young patients and allows us to hypothesize that hydroxyurea may preserve organ function in SCA. Children in this study had stable GFR values, significant decreases in TCD velocities, and stable MRI/MRA during a time interval when organ dysfunction develops.

In addition, children had beneficial changes in hematological values, increases in growth parameters, and reported less impact of disease on family after two years of hydroxyurea therapy. We anticipate more definitive data from the ongoing BABY HUG trial that tests formally the hypothesis that hydroxyurea prevents organ damage in young children with SCA.

Acknowledgments

The study was supported by the NHLBI grants 5K23HL4005 (SZ), K24HL068230 (RW), U54HL070769 (CT) and the American Lebanese Syrian Associated Charities (RW). The authors acknowledge Dr. Daniel Laskowitz for assistance with TCD examinations, Jacqueline Davis and Tracy Kelly for clinical care, and Maggie Hood and Amanda Mandy for data entry.

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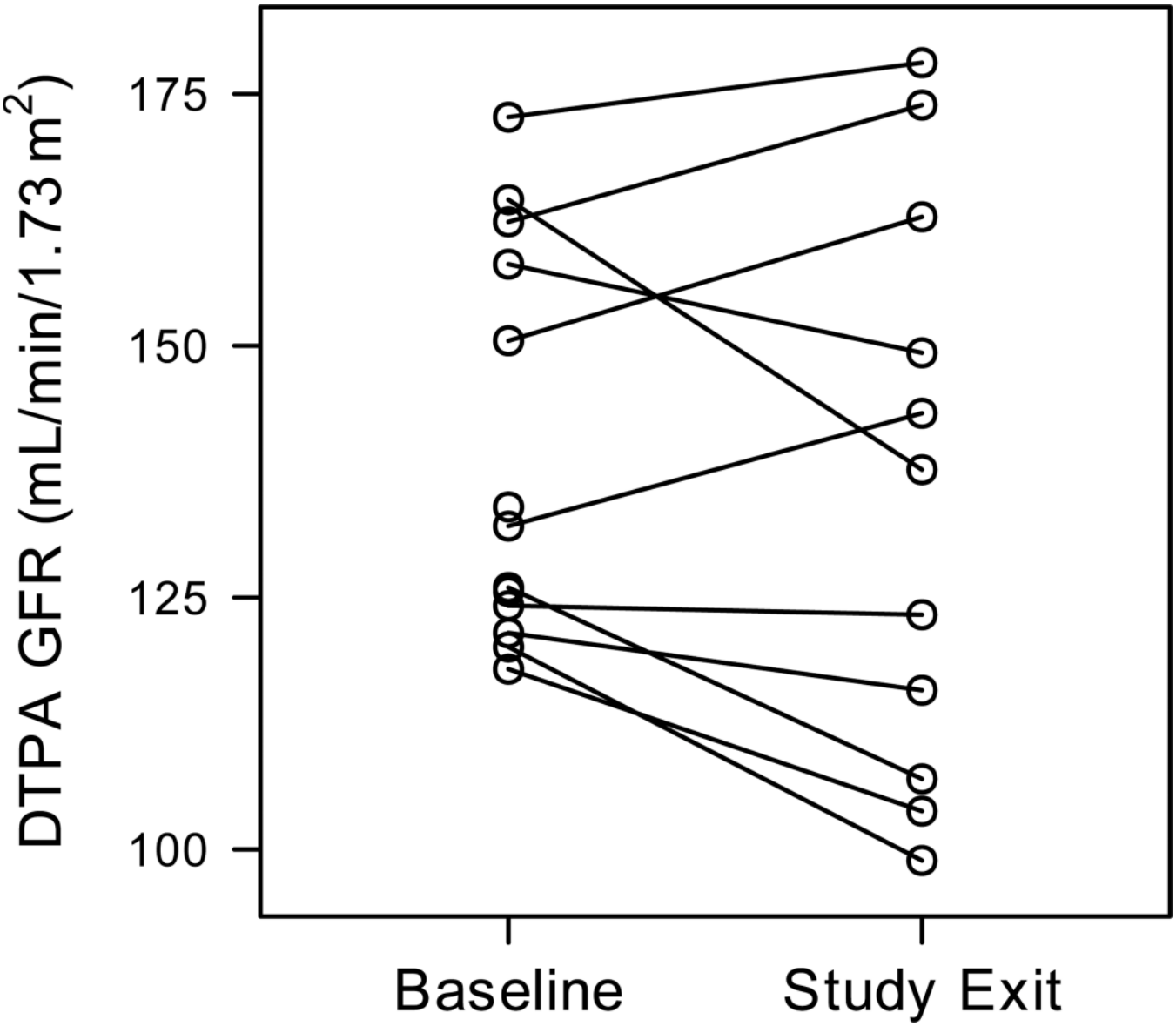

Figure 1.

DTPA glomerular filtration rate (GFR) changes in Toddler HUG. Lines connect data for individual subjects. The difference between baseline and study exit GFR by DTPA clearance was 5.1 ± 14.1 mL/min/1.73 m^2 (p=0.26).

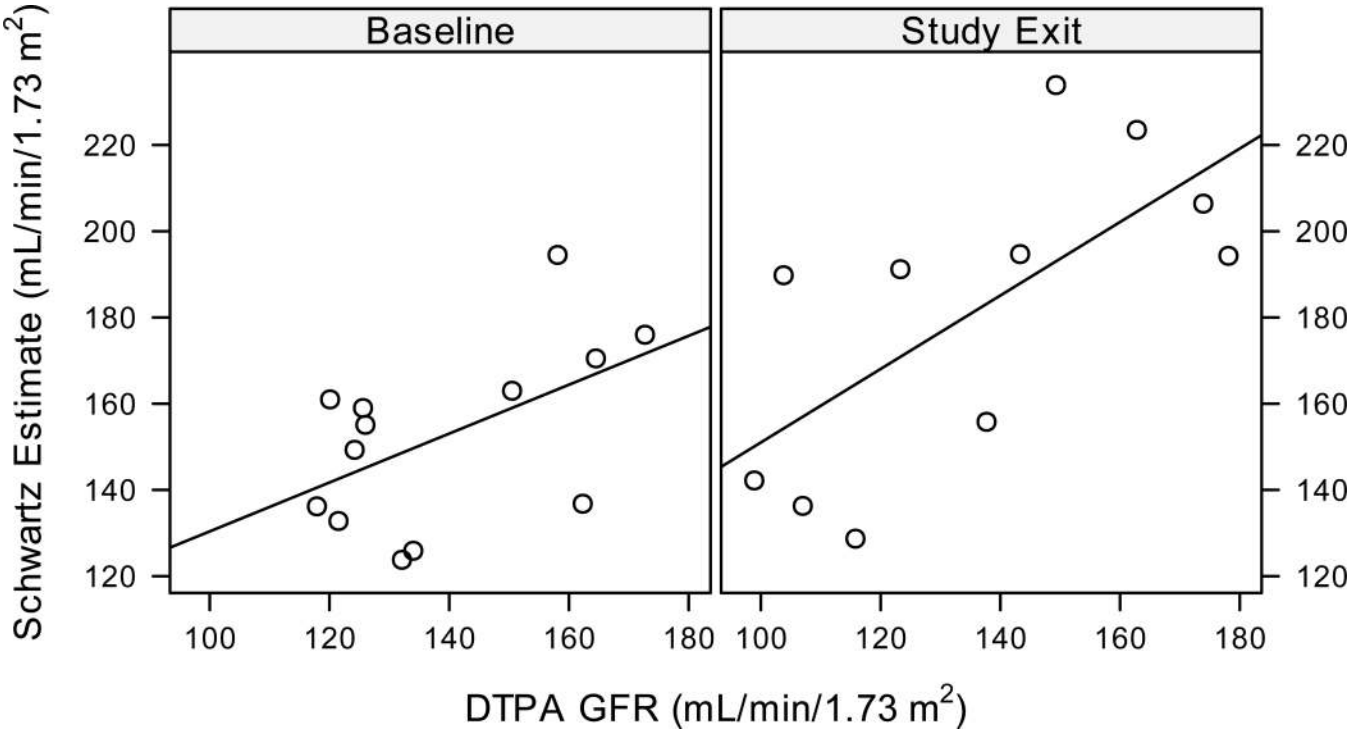

Figure 2.

Statistical associations between glomerular filtration rate (GFR) by quantitative DTPA clearance and Schwartz estimate, both at study baseline before hydroxyurea treatment and at study exit while on hydroxyurea. The correlation between GFR quantitation by DTPA clearance at baseline and study exit were 0.53 ($p=0.06$) and 0.68 ($p<0.05$), respectively.

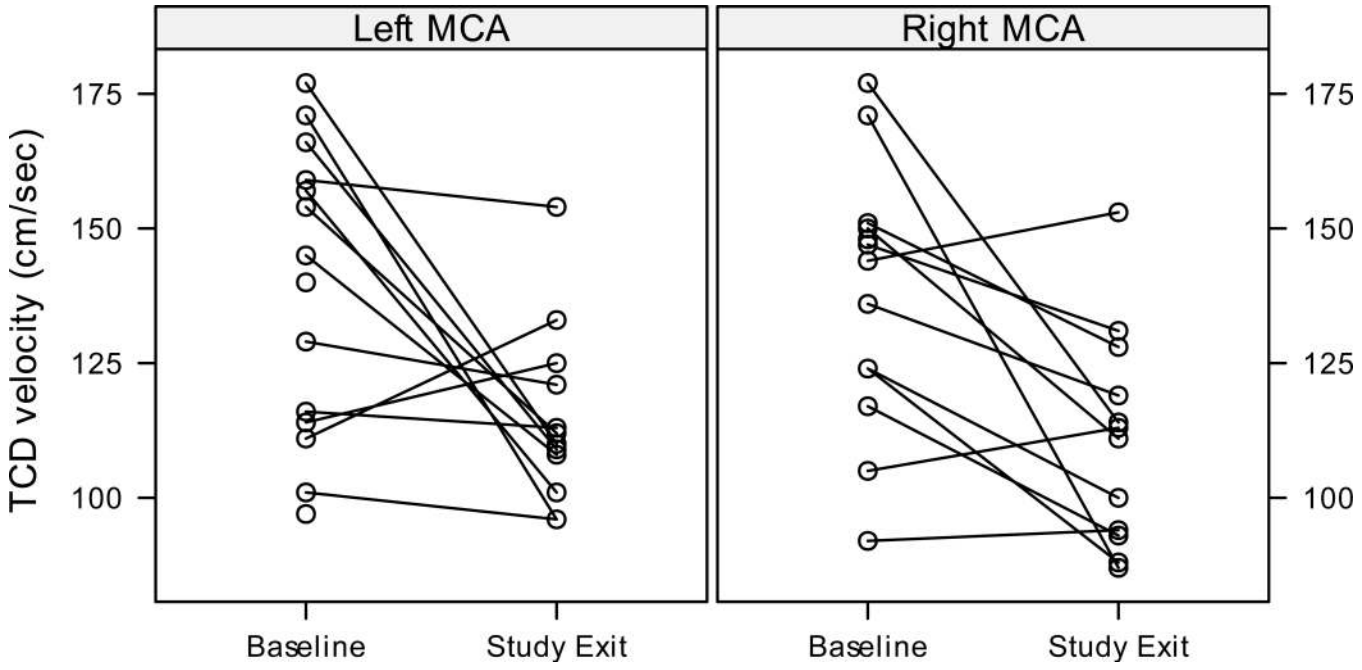

Figure 3.

Maximal mean left and right middle cerebral artery (MCA) transcranial doppler (TCD) velocities at study baseline before hydroxyurea treatment and at study exit while on hydroxyurea. Lines connect data for individual subjects. The TCD velocities in both the right and left MCA are significantly lower after 2 years of hydroxyurea treatment (study exit) than the values at study entry (baseline).

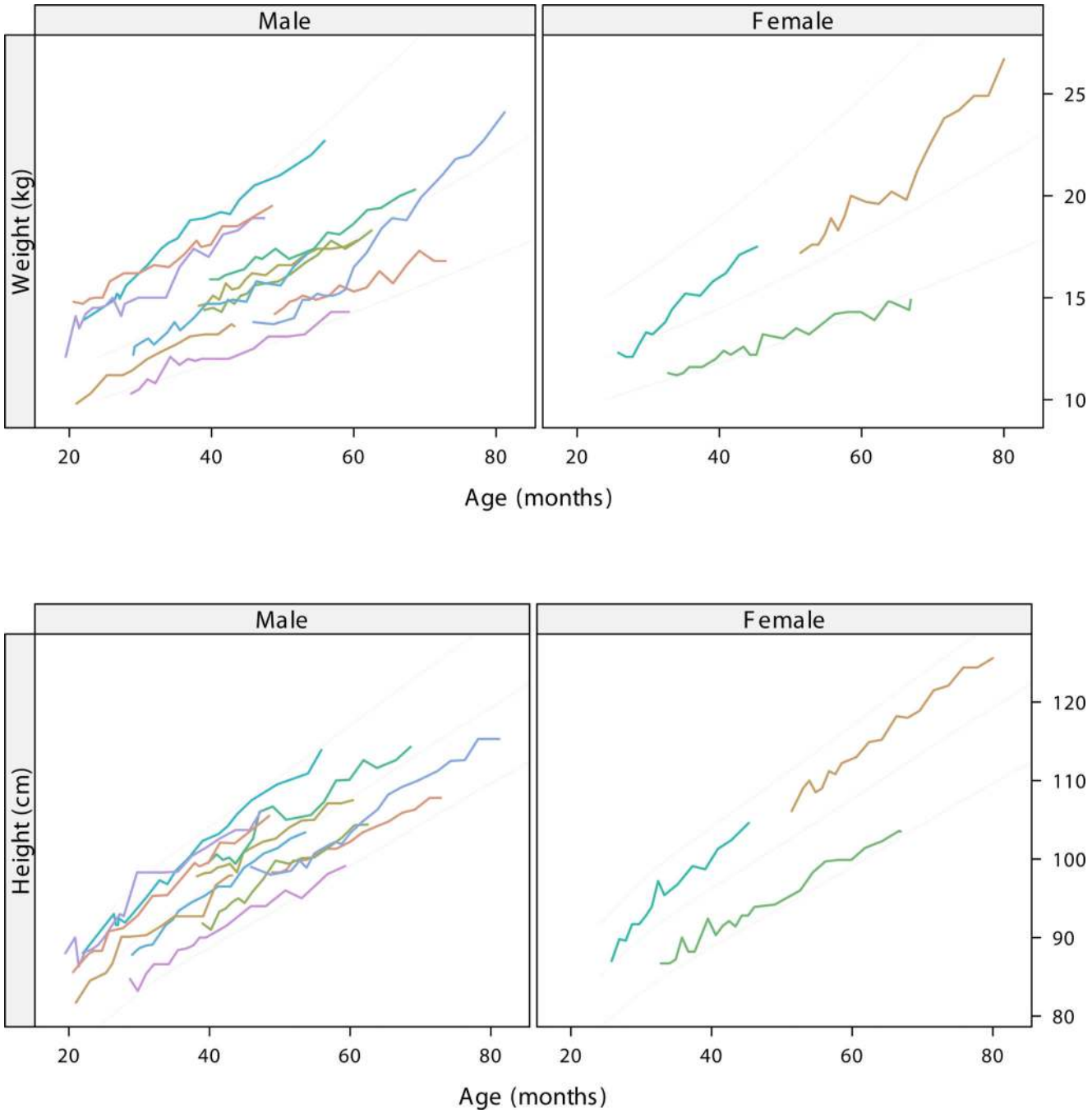

Figure 4.

Individual growth curves for young children with sickle cell anemia who received hydroxyurea at maximum tolerated dose for 2 years. The grey lines represent the 3rd, 50th and 97th percentiles for weight and height of a healthy population. Male and female children either maintained or increased growth parameters.

Table I

Baseline clinical characteristics and organ function.

Age, mo	Hb, g/dL	HbF, %	TCD, cm/sec right/left	MRI/MRA	GFR, mL/min/1.73 m^2
21	10.6	38.6	147, 114	nl, nl	132.1
21	8.2	18.9	105, 111	nl, nl	-
23	9.0	15.5	148, 140	-	125.6
27	8.4	19.2	117, 97	nl, nl	134.0
27	7.5	24.4	92, 101	nl, nl	164.5
29	8.8	16.3	124, 129	nl, nl	120.1
30	6.9	7.9	136, 116	nl, nl	126.0
34	7.2	9.8	144, 159	nl, abnl	117.9
39	6.5	4.4	124, 145	nl, nl	150.5
40	8.1	12.9	171, 171	nl, nl	124.2
41	6.4	4.8	177, 166	nl, abnl	162.3
49	8.0	8.6	150, 177	abnl, nl	172.7
52	8.5	10.1	117, 157	nl, nl	121.5
53	8.4	13.6	151, 154	nl, nl	158.1

Pediatr Blood Cancer. Author manuscript; available in PMC 2017 September 15.

Table II

Hematological effects of hydroxyurea at maximum tolerated dose in 14 young children with sickle cell anemia.

	Baseline	Study Exit	Change from Baseline to Study Exit (95% CI)	P value[¤]
Hemoglobin, g/dL	8.0 ± 1.0	9.5 ± 1.0	1.5 (0.9 to 2.0)	<0.001
MCV, fL	84 ± 8	99 ± 12	15 (11 to 20)	<0.001
ANC, 10^6/L	5614 ± 2898	3024 ± 1409	−2591 (−4361 to −821)	<0.01
Platelets, 10^9/L	357 ± 115	310 ± 166	−47 (−137 to 44)	0.29
Reticulocytes, 10^9/L	365 ± 130	166 ± 73.1	−198 (−274 to −122)	<0.001
Bilirubin, mg/dL	2.2 ± 0.9	1.3 ± 0.6	−0.9 (−1.5 to −0.4)	<0.01
HbF, %	14.6 ± 9.0	25.9 ± 6.6	11.2 (7.1 to 15.4)	<0.001

Laboratory data are shown as the mean ± SD. Baseline indicates prior to hydroxyurea therapy. Study exit indicates on hydroxyurea therapy for approximately two years.

[¤] Student's paired t test.

Table III

Cognitive and HRQL measures for 14 young children with sickle cell anemia treated with hydroxyurea.

	Baseline	Midpoint	Study Exit	P value[¤]
Cognitive standard score[†]	94.2 ± 19.9	—	96.2 ± 22.9	0.70
HRQL standard score[‡]	80.7 ± 10.7	81.1 ± 9.9	82.8 ± 12.1	0.67
IOF total impact score[//]	43.2 ± 7.6	39.7 ± 7.3	32.9 ± 6.9	0.001

Data are mean scores ± SD.

— indicates that there Cognitive standard scores were not collected at this timepoint.

[¤] Linear mixed model with trend test.

[†] The Cognitive standard score is derived from the McCarthy CGI or Bayley MDI.

[‡] The HRQL standard score is derived from the PedsQL™ Parent Report for Toddlers ages 2–4 years Version 4.0.

[//] The IOF total impact score is derived from the IOF scale.