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Influence of Severity of Anemia on Clinical Findings in Infants with Sickle Cell Anemia: Analyses from the BABY HUG Study

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Abstract

Background—Clinical complications of sickle cell anemia begin in infancy. BABY HUG (ClinicalTrials.gov, NCT00006400) was a NHLBI-NICHD supported randomized phase III placebo-controlled trial of hydroxyurea (HU) in infants (recruited at 9–18 months) unselected for clinical severity with sickle cell anemia. This secondary analysis of data from BABY HUG examines the influence of anemia on the incidence of sickle cell related complications, and the impact of hydroxyurea therapy in altering these events by comparing children with lower (<25th percentile) and higher (>75th percentile) hemoglobin concentrations at study entry.

Procedure—Infants were categorized by: 1) age-adjusted hemoglobin quartiles as determined by higher (Hi) and lower (Lo) hemoglobin concentrations at study entry (9 to12 months old: <8.0 gm/dL and >10.0gm/dL; 12 to 18 months old: <8.1 gm/dL and >9.9gm/dL) and 2) treatment arm (hydroxyurea or placebo). Four subgroups were created: placebo (PL) LoHb (n=25), PL HiHb (n=27), hydroxyurea (HU) LoHb (n=21), and HU HiHb (n=18). The primary and secondary endpoints of BABY HUG were analyzed by subgroup.

Results—Infants with lower hemoglobin at baseline were more likely to have a higher incidence of clinical events (acute chest syndrome, pain crisis, fever) as well as higher TCD velocities and lower neuropsychological scores at study exit. Hydroxyurea reduced the incidence of these findings.

Conclusion—Infants with more severe anemia are at risk for increased clinical events that may be prevented by early initiation of hydroxyurea.

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Keywords

Sickle Cell Anemia; Hydroxyurea; Acute Chest Syndrome; Pain; Transcranial Doppler; Renal; Spleen

Introduction

Persons with sickle cell anemia (SCA) are at risk for organ failure and clinical events that develop over their lifetime.[1] Beginning in infancy, they frequently require hospitalization for pain crisis, fever, acute chest syndrome, and CNS injury.[2–7] Severe anemia is a prognostic factor for adverse outcomes, both in children and adults.[8–11] Recently, two clinical phenotypes of sickle cell disease have been proposed: more severe anemia secondary to hyperhemolysis associated with pulmonary hypertension, leg ulceration, stroke and priapism; and higher hemoglobin concentration with greater risk for episodes of pain, acute chest syndrome, avascular necrosis of the hip and retinopathy.[12–14] Hemoglobin concentration may affect disease expression in SCA.

Hydroxyurea therapy raises hemoglobin concentration, reduces the frequency of pain crisis, acute chest syndrome, and hospitalizations, and improves overall survival.[15–18] BABY HUG (ClinicalTrials.gov, NCT00006400), a NHLBI-NICHD supported phase III randomized placebo-controlled trial, was designed to examine the effect of hydroxyurea on reduction of damage to the kidneys and spleen in infants with SCA. While the primary endpoints of the study [^{99m}Tc-sulfur colloid uptake on liver-spleen scan and glomerular filtration rate (GFR) by ^{99m}Tc-DTPA clearance] were not significantly impacted by hydroxyurea therapy, numerous secondary endpoints strongly suggested clinical benefit with hydroxyurea administration.[19]

To determine whether low and high hemoglobin concentrations during infancy were associated with specific clinical complications, we performed a secondary analysis of BABY HUG data. We hypothesized that subgroups of infants treated with placebo, defined by the lowest and highest quartiles of baseline hemoglobin concentration, would differ from one another in the frequency of sickle cell-related complications. We further hypothesized that hydroxyurea would decrease the incidence of sickle cell-related complications of SCA in those with the lowest baseline hemoglobin concentrations when compared to the most anemic placebo subjects.

Methods

BABY HUG subjects with Hb SS (186) or Sβ^0-thalassemia (6) were randomized at ages 9 – 18 months to receive hydroxyurea (20 mg/kg/d) (N=96) or placebo (N=97) for 2 years.[20] Hemoglobin concentrations obtained at screening visits for eligibility and before randomization were used to determine the 25th and 75th hemoglobin percentile values based on age. The baseline hemoglobin concentrations demarcating the lowest and highest quartiles were: <8.0 gm/dL and >10.0gm/dL for ages 9 to 12 months, and <8.1 gm/dL and >9.9gm/dL for ages   12 to 18 months. Subjects were classified according to: 1) age-adjusted baseline hemoglobin [lowest (LoHb) and highest (HiHb) quartiles] and 2) randomized treatment arm hydroxyurea (HU) or [9,12]placebo (PL). Primary and secondary endpoints of BABY HUG were re-analyzed according to these four groups: PL LoHb (n=25), PL HiHb (n=27), HU LoHb (n=21), and HU HiHb (n=18). Methodology for ^{99}Tc sulfur colloid liver/ spleen scan and determination of GFR by ^{99m}Tc-DTPA clearance, erythrocyte pit counts, quantitation of Howell-Jolly bodies, and definitions of adverse events are reported

elsewhere. [19] Kidney and spleen endpoints were analyzed as continuous variables or as categorical variables. All adverse events were summarized as rates per person-year.

Comparison of change from baseline to exit was carried out by using two-sample t-tests for continuous variables. The Pearson chi-square test was used for categorical variables represented as a change from baseline (Y, N). Relative risks were estimated using the Poisson regression model and the corresponding p values were calculated when comparing the rates among different groups. Mixed model analysis was used to perform analyses of serially collected laboratory measurements. The Generalized Estimating Equation (GEE) method was used to analyze serially-collected categorical data which, like the mixed model analysis, also accounted for inter-subject correlations. Data analysis was performed using the statistical package SAS version 9.2 (SAS Inc., Cary, NC).

Results

Primary Endpoints

At study exit, the BABY HUG primary endpoints of preservation of spleen or renal function did not differ statistically between the PL LoHb and PL HiHb groups (Table I). Subjects in the PL LoHb group did not demonstrate increased glomerular hyperfiltration when compared to those in the HU LoHb group at study exit (p = 0.38).

Secondary Endpoints

Surrogate Markers of the Primary Spleen Endpoint: At study entry (mean age 13 months), pit counts were significantly higher in the PL LoHb group than in the PL HiHb group (p=0.02) and the mean value for the PL LoHb group was above 3.5 percent, the established threshold for abnormal spleen function(Table II). [21] The mean pit count nearly doubled over the study period in the PL LoHb group (7.4% to 14.0%), while the pit count decreased slightly in the HU LoHb group. (7.8% to 6.3%). In the HiHb groups, both the PL HiHb and HU HiHb subjects had exit mean pit counts 3.5 percent.

Clinical Complications of Sickle Cell Anemia

Acute Chest Syndrome—PL LoHb subjects had a much higher incidence and relative risk of acute chest syndrome than PL HiHb infants (p=0.008); hydroxyurea therapy significantly reduced the incidence of acute chest syndrome in those with low hemoglobin levels (PL LoHb vs. HU LoHb; p=0.02) (Table III).

Pain—PL LoHb subjects had a higher incidence and relative risk of admission for painful crisis than PL HiHb infants (p=0.04) and a trend toward a higher risk of dactylitis (p=0.07) (Table III). Hydroxyurea therapy significantly reduced the incidence of pain and dactylitis in subjects with low hemoglobin levels (PL LoHb vs. HU LoHb; p<0.001). Among the four subgroups, PL LoHb had the highest incidence of pain and HU HiHb the lowest.

Fever—PL LoHb subjects had a higher incidence and relative risk of fever than PL HiHb subjects (p=0.02) (Table III). When the two LoHb groups were compared, HU did not alter frequency of febrile episodes (p=0.10). The incidence of bacteremia/sepsis was too low to compare groups.

Laboratory values—PL LoHb infants had higher study average and exit white blood cell (WBC), absolute neutrophil, and platelet counts than those of PL HiHb infants. Hydroxyurea therapy resulted in significantly lower values of these blood counts. PL HiHb infants had similar WBC, absolute neutrophil, and platelet counts compared to those of infants receiving hydroxyurea.

Neurologic measures—At baseline, LoHb infants had higher TCD velocities than HiHb infants. Patients treated with hydroxyurea had less of a rise in TCD velocity during randomized study treatment as compared to the placebo groups. Results of neurocognitive testing (Bayley Scales of Infant Development) were not statistically different between groups; however, a trend toward a lower performance developmental index (fine and gross motor skills), but not a lower mental development index (cognitive skills and attention), was observed in PL LoHb children as compared to HU LoHb.

Discussion

The BABY HUG randomized trial provided evidence that infants with HbSS and $S\beta^0$ thalassemia randomized to hydroxyurea received a clinical benefit. This analysis indicates that infants with lower hemoglobin concentrations are at greater risk for certain sickle cell-related complications during early childhood, and that this extra risk was largely eliminated by treatment with hydroxyurea. These findings are consistent with murine models of sickle cell anemia, which have demonstrated that organ damage is associated with lower hemoglobin levels and that correction of anemia through fetal hemoglobin induction can prevent organ pathology.[22]

Contrary to previous reports in older children and adults associating risk of pain and ACS with modest anemia, [6,12,23] our study showed that infants with lowest hemoglobin levels are at higher risk for developing both complications, a risk that can be reduced with hydroxyurea therapy. Though not confirmed by the Dallas Newborn Cohort, the Cooperative Study of Sickle Cell Disease found that severe anemia [baseline hemoglobin concentration less than the fifth percentile (7 gm/dL) during the second year of life predicted poorer outcomes (frequent pain and ACS; stroke; and death) over the first decade.[10,24] In BABY HUG, a subgroup of infants with more modest anemia (< the 25th percentile) also experienced increased pain and ACS, evident during just the first three to four years of life; ongoing follow-up of the BABY HUG cohort should clarify whether or not these risks are durable through the first decade.

Lower baseline hemoglobin concentration is associated with higher white blood cell, absolute neutrophil, and platelet counts. Interestingly, PL HiHb infants had a mean lower WBC, ANC and platelet counts than HU LoHb infants. This association of anemia with leukocytosis could be significant, as previous studies have demonstrated elevated WBC to be an adverse prognostic factor in children and adults.[6,9,10,23] The role of anemia in potentially causing increased inflammation and adverse events needs further evaluation and clarification.

Our data demonstrate that the effect of low hemoglobin on spleen function and TCD velocity is apparent at a very young age (9–12 months); and that the more severe clinical course predicted by low hemoglobin can be ameliorated by treatment with hydroxyurea. These risks associated with anemia during infancy should especially prompt consideration of the early use of hydroxyurea for children with very low hemoglobin levels in this age group, although the benefits of hydroxyurea demonstrated in BABY HUG extended across the entire study population. Studies that prospectively target infants with lower hemoglobin concentration might more specifically demonstrate the therapeutic benefit of hydroxyurea in ameliorating the impact of severe anemia on organ function.

Acknowledgments

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Table I

Spleen and Renal Primary Endpoints

Primary Endpoints	PL LoHb	PL HiHb	HU LoHb	HU HiHb	PL LoHb vs. PL HiHb (P-Value)	PL LoHb vs. HU LoHb (P-Value)	PL HiHb vs. HU HiHb (P-Value)	HU LoHb vs. HU HiHb (P-Value)
Exit Spleen Scan (n)								
Worse	8	7	7	5	0.205	1.000	1.000	0.473
Not Worse	8	17	8	11	0.205	1.000	1.000	0.473
GFR (mean, mL/min/1.73 m²)								
Baseline	122.6	120.9	117.6	135.6	0.881	0.688	0.255	0.197
Exit	158.5	141.8	145.7	143.6	0.222	0.377	0.902	0.886
Exit- baseline (Δ)	31.2	21.8	29.6	12.7	0.632	0.943	0.678	0.472

PL LoHb= Placebo arm, lower hemoglobin quartile. PL HiHb= Placebo arm, higher hemoglobin quartile. HU LoHb= Hydroxyurea arm, lower hemoglobin quartile. HU HiHb= Hydroxyurea arm, higher hemoglobin quartile. GFR= glomerular filtration rate. n= number of patients. Δ= difference

Table II

Secondary Endpoints

Surrogate Markers of Spleen Function	PL LoHb	PL HiHb	HU LoHb	HU HiHb	PL LoHb vs. PL HiHb (P-Value)	PL LoHb vs. HU LoHb (P-Value)	PL HiHb vs. HU HiHb (P-Value)	HU LoHb vs. HU HiHb (P-Value)
Howell-Jolly Bodies (per 10^6 RBC) (baseline)	942	56	1360	87	<0.001	0.042	0.886	<0.001
Howell-Jolly Bodies (per 10^6 RBC) (exit)	2004	743	2410	500	<0.001	0.180	0.292	<0.001
Howell-Jolly Bodies (per 10^6 RBC) exit-baseline	1062	687	1050	413	0.107	0.961	0.281	0.019
Pit cell Count % (baseline)	7.4	1.1	7.8	1.9	<0.001	0.202	0.524	<0.001
Pit cell Count % (exit)	14.0	3.5	6.3	3.1	<0.001	<0.001	0.820	0.089
Pit cell count% exit-baseline	6.6	2.4	−1.5	1.1	0.024	<0.001	0.529	0.215

PL LoHb= Placebo arm, lower hemoglobin quartile. PL HiHb= Placebo arm, higher hemoglobin quartile. HU LoHb= Hydroxyurea arm, lower hemoglobin quartile. HU HiHb= Hydroxyurea arm, higher hemoglobin quartile. RBC= red blood cell.

Table III

Clinical Complications

Incidence (events person-year)	PL LoHb	PL HiHb	HU LoHb	HU HiHb	PL LoHb vs. PL HiHb		PL LoHb vs. HU LoHb		PL HiHb vs.HU HiHb		HU LoHb vs. HU HiHb	
					RR (CI)	p-value	RR (CI)	p-value	RR (CI)	p-value	RR (CI)	p-value
Dactylitis	0.78	0.49	0.17	0	1.58 (0.96,2.61)	0.07	4.62 (2.06,10.37)	<0.001	0	1.000	0	1.000
Pain	2.36	1.76	0.96	0.58	1.34 (1.02, 1.76)	0.04	2.44 (1.71, 3.51)	<0.001	3.05 (1.86, 4.99)	<0.001	1.67 (0.97, 2.88)	0.067
Acute Chest Syndrome	0.30	0.02	0.02	0.06	15.6 (2.05, 118.4)	0.008	12.24 (1.61, 93.11)	0.016	0.31 (0.03, 3.43)	0.340	0.40 (0.04, 4.36)	0.449
Fever >101.5	2.13	1.50	1.64	2.16	1.42 (1.06, 1.91)	0.019	1.30 (0.96, 1.77)	0.095	0.69 (0.50, 0.95)	0.025	0.76 (0.54, 1.06)	0.103
Sepsis	0.04	0.04	0	0	1.11 (0.16, 7.90)	0.92	0	1.000	0	1.000	-	1.000

PL LoHb= Placebo arm, lower hemoglobin quartile. PL HiHb= Placebo arm, higher hemoglobin quartile. HU LoHb= Hydroxyurea arm, lower hemoglobin quartile. HU HiHb= Hydroxyurea arm, higher hemoglobin quartile. RR= relative risk. CI= 95% confidence interval.