

Hydroxyurea Is Associated With Lower Costs of Care of Young Children With Sickle Cell Anemia

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KEY WORDS

hydroxyurea, medical costs, young children, sickle cell anemia

ABBREVIATIONS

ACS—acute chest syndrome

CRF—case report form

ED—emergency department

HbF—hemoglobin F

HbSS—sickle cell anemia

HSN—hospitalization

ICD-9-CM—International Classification of Diseases, Ninth Revision, Clinical Modification

LOS—length of stay

MSH—Multi-Center Study of Hydroxyurea

SpS—splenic sequestration

TX—transfusions

Dr Wang was the overall principal investigator of the BABY HUG study and made substantial contributions to the concept of this analysis and interpretation of the data; he drafted the article and revised it critically for important intellectual content; Drs Grosse, Boulet, and Oyeku made substantial contributions to the concept and design of the study, facilitated use of the MarketScan data, and drafted the article and revised it critically for important intellectual content; Drs Thompson and Luo, and Ms Fish led the collection and analysis of the BABY HUG data and drafted the statistical sections of the article; Drs Miller and Casella were principal investigators in the BABY HUG study and revised the article critically for important intellectual content; and all authors had final approval of the version submitted.

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WHAT'S KNOWN ON THIS SUBJECT: Persons with sickle cell anemia are known to have increased medical expenses, but little is known about the effects of hydroxyurea treatment on costs. In adults with severe sickle cell anemia, hydroxyurea has been reported to reduce expenses from hospitalization.



WHAT THIS STUDY ADDS: In this randomized placebo-controlled prospective multicenter trial of hydroxyurea in very young children with sickle cell anemia, not selected for severity, hydroxyurea was associated with significant medical cost savings due to a reduction in hospitalization expenses.

abstract



BACKGROUND AND OBJECTIVE: In the BABY HUG trial, young children with sickle cell anemia randomized to receive hydroxyurea had fewer episodes of pain, hospitalization, and transfusions. With anticipated broader use of hydroxyurea in this population, we sought to estimate medical costs of care in treated versus untreated children.

METHODS: The BABY HUG database was used to compare inpatient events in subjects receiving hydroxyurea with those receiving placebo. Unit costs were estimated from the 2009 MarketScan Multi-state Medicaid Database for children with sickle cell disease, aged 1 to 3 years. Inpatient costs were based on length of hospital stay, modified by the occurrence of acute chest syndrome, splenic sequestration, or transfusion. Outpatient expenses were based on the schedule required for BABY HUG and a “standard” schedule for 1- to 3-year-olds with sickle cell anemia.

RESULTS: There were 232 hospitalizations in the subjects receiving hydroxyurea and 324 in those on placebo; length of hospital stay was similar in the 2 groups. Estimated outpatient expenses were greater in those receiving hydroxyurea, but these were overshadowed by inpatient costs. The total estimated annual cost for those on hydroxyurea (\$11 072) was 21% less than the cost of those on placebo (\$13 962; $P = .038$).

CONCLUSIONS: Savings on inpatient care resulted in a significantly lower overall estimated medical care cost for young children with sickle cell anemia who were receiving hydroxyurea compared with those receiving placebo. Because cost savings are likely to increase with age, these data provide additional support for broad use of hydroxyurea treatment in this population. *Pediatrics* 2013;132:677–683

Hydroxyurea is an inhibitor of ribonucleotide reductase that increases fetal hemoglobin (HbF) in red blood cells and decreases the frequency of pain events, acute chest syndrome (ACS), hospitalization (HSN), and transfusion (TX) as demonstrated in the Multi-Center Study of Hydroxyurea (MSH) in adults with clinically severe sickle cell anemia.¹ Similar effects have been seen in school-age children and adolescents with frequent vaso-occlusive events, leading to widespread use of hydroxyurea by pediatric sickle cell centers for this indication.^{2,3} Promoting the appropriate use of hydroxyurea is a promising way to improve health outcomes among patients with sickle cell disease, but barriers to its widespread use need to be addressed.^{4,5}

The BABY HUG study was an institutional review board–approved National Institutes of Health–funded multicenter randomized double-blinded trial of hydroxyurea in very young children with sickle cell anemia (HbSS or HbS β^0 thalassemia), 9 to 18 months old at enrollment, who were not selected for clinical severity.⁶ Subjects received oral hydroxyurea at a dose of 20 mg/kg/day or placebo for 2 years. Although the study failed to show significant differences in the primary endpoints for spleen and renal function between the hydroxyurea group and the placebo group, subjects receiving the drug had fewer episodes of pain, ACS and dactylitis and less frequent HSN and TX ($P < .001$ – $.05$).⁶ In addition, hydroxyurea-treated subjects had higher hemoglobin and HbF levels and lower white blood cell and reticulocyte counts. Hydroxyurea was not associated with significant toxicity other than expected mild-moderate neutropenia. It was concluded, “on the basis of the safety and efficacy data from this trial, hydroxyurea can now be considered for all children with sickle cell anemia starting at an early age.”⁶ Other reviews and commentaries also have

recommended broader consideration of hydroxyurea for children with sickle cell anemia.^{7,8}

A post hoc analysis of MSH data demonstrated that despite the need for frequent outpatient visits for dose monitoring, use of hydroxyurea reduced costs associated with care of adults with moderate to severe sickle cell anemia.⁹ In view of the anticipated greater use of hydroxyurea in the pediatric sickle cell population, perhaps including children with mild or pre-symptomatic disease, we retrospectively examined estimated costs for hospital admissions and routine care in the hydroxyurea and placebo-treated subjects in the BABY HUG study to assess the net impact of hydroxyurea on overall medical costs. Previously published analyses of observational data have yielded mixed results regarding relative medical costs among patients using hydroxyurea, which may reflect differences in disease severity.^{10–12} Because the BABY HUG study was a blinded randomized trial, it provided a unique opportunity to assess differences in medical costs, while controlling for differences in disease severity.

METHODS

This is a retrospective economic evaluation of the BABY HUG study conducted from the public health care payer (Medicaid) perspective. The analysis uses estimates of total medical expenditures for Medicaid-enrolled children with sickle cell anemia who were treated with hydroxyurea during the BABY HUG trial. Medical expenditures in the analysis include inpatient, outpatient, and medication costs. The analysis does not include costs associated with family caregiver time or travel associated with receipt of medical care.

The BABY HUG database (C-TASC, Owings Mills, MD) was used to compare numbers

and characteristics of inpatient events in subjects receiving hydroxyurea to those receiving placebo.⁶ A revised case report form (CRF) used between February 2006 and September 2009 (the end of the study) allowed data capture in sufficient detail for the analysis of serious events (including ACS, splenic sequestration [SpS], sepsis, and stroke), reportable treatments, and lengths of HSN (admission and discharge dates), but did not include emergency department (ED) data. Hospitalizations during this period accounted for 77% of those occurring over the entire study period, which began in October 2003.

As is standard in economic evaluations associated with randomized clinical trials, the quantities of health care services used were multiplied by standardized unit costs to estimate medical costs.¹³ Available national estimates of average costs of HSN, either overall or relative to length of stay (LOS), were used. As noted, data were restricted to inpatient stays and did not include “ED-only” visits. Subjects in the BABY HUG trial were classified into 6 mutually exclusive categories based on the more common significant complications reported on the CRF for a given hospitalization: HSN alone, HSN + TX, HSN + ACS, HSN + ACS + TX, HSN + SpS, and HSN + SpS + TX. Data from the trial were used to calculate the average LOS per hospitalization for patients in the hydroxyurea group and in the placebo group for each of these 6 categories.

Approximately two-thirds of children with sickle cell disease are covered by public insurance.¹⁴ Because hospital costs are highly variable depending on the intensity of services delivered, it was decided to use billing data for hospital services received by publicly insured young children with sickle cell anemia relative to complications and procedures recorded in health insurance

claims records.¹⁴ The MarketScan Medicaid database consists of a sample of claims and encounter records from 12 anonymous state Medicaid and Children's Health Insurance Plan programs. MarketScan Medicaid claims data have previously been used to assess health care utilization and expenditures for publicly insured US children with sickle cell disease.^{15,16} In our analysis, unit costs per hospitalization were estimated from the 2009 MarketScan Multi-state Medicaid Research Databases Inpatient Services file (Truven Health Analytics) for children aged 1 to 3 years with *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* codes 282.61 or 282.62 present in any diagnostic field, indicating HbSS disease without or with crisis, respectively. The measure of cost was the arithmetic mean total payment received by providers, including both payments by health plans and individuals (copays and deductibles). MarketScan costs for inpatient admissions included the costs of ED visits from the same institution that resulted in admissions. Inpatient admissions with a length of stay >15 days and those with zero expenditures were excluded from the analysis ($n = 9$). Among 655 total admissions of children with HbSS in the MarketScan analysis, ~79% included an ED visit.

Predicted costs for each of the 6 categories of hospitalizations from the BABY HUG trial were estimated by using MarketScan Medicaid data. A generalized linear model with a logarithmic link function and γ variance was used to estimate hospitalization costs per day for inpatient admissions of patients with HbSS classified based on ICD-9 and Current Procedural Terminology codes. The covariates included in the model were hospital LOS, whether ≥ 1 TX (ICD-9 codes 99.00–99.09 and Current Procedural Terminology codes 36430, 36440, 36455)

were administered, concurrent SpS (ICD-9 code 289.52) and/or ACS (ICD-9 codes 480–486, 517.3), and the interaction of LOS with TX, SpS, and/or ACS. Marginal effects were used to estimate mean costs per hospitalization at specified values of covariates.

The average LOS from the BABY HUG study multiplied by the estimated daily cost based on the analysis of MarketScan data for the 6 categories gave the estimated average cost for a patient's care in that hospitalization category. The number of events in each hospitalization category was determined from the CRFs. Multiplying the average cost by the number of events yielded the total cost for each particular type of hospitalization. From these data, the total estimated cost of hospitalization for each group was calculated and divided by the number of hospitalization events to obtain an average cost per hospitalization for hydroxyurea subjects and placebo subjects. Using the number of hospitalizations during the total course of the trial, the estimated total cost of all hospitalizations in each group was calculated, as well as the estimated hospitalization cost per patient year.

Outpatient expenses for children receiving hydroxyurea were estimated on the basis of the schedule required for the BABY HUG study (and recommended for clinical use) and supported by a survey of pediatric hematologists, which found that the majority of providers see patients being treated with hydroxyurea on a monthly basis.¹⁷ The numbers of clinic visits, blood counts (complete blood count, reticulocyte count, HbF, chemistry panel), and hydroxyurea prescriptions for patients receiving hydroxyurea were used. Outpatient expenses for the placebo group were not based on actual costs incurred. Because children receiving placebo adhered to the same visit schedule as those receiving hydroxy-

urea in this blinded trial, an outpatient schedule for untreated 1- to 3-year-olds with sickle cell anemia was used to estimate their expenses based on "standard management" protocols at 3 pediatric sickle cell centers in the United States (St Jude Children's Research Hospital, Children's Hospital at Montefiore, State University of New York—Downstate).

The estimated cost of liquid formulation of hydroxyurea was based on averaged data from pharmacies at 2 institutions (Children's Hospital of Atlanta and St Jude Children's Research Hospital) and commercial pharmacies serving patients at State University of New York—Downstate and Children's Hospital at Montefiore. Using 2009 MarketScan Multi-State Medicaid outpatient claims data for children with HbSS, aged 1 to 3 years, estimated total outpatient costs per hydroxyurea-treated or standard care sickle cell patient were calculated. These costs were divided by 2 to obtain an estimated average outpatient cost per patient per year for hydroxyurea treatment in the BABY HUG study and the hypothetical cost of standard care for untreated patients.

Finally, predicted inpatient and outpatient expenses were combined to yield estimated annual mean costs for 1- to 3-year-old children with sickle cell anemia who were receiving hydroxyurea or placebo/standard care.

The costs for the hydroxyurea and placebo groups were compared by using a Wilcoxon rank-sum statistic because the estimated cost distribution was skewed.

RESULTS

One hundred ninety-three subjects were randomized in the BABY HUG trial. Baseline characteristics of the study population have been reported with no significant differences in age, gender, genotype, clinical severity, laboratory values, or physical findings between the

2 groups.⁶ From the 96 subjects who were randomized to receive hydroxyurea (including 83 who completed the trial), there were 189 patient-years of evaluable follow-up data. The 97 subjects who were randomized to receive placebo (including 84 who completed the trial) provided 186 patient-years of data. Seventy-four percent of subjects (142 of 193) were covered by Medicaid or a state insurance program.

Inpatient Costs

The total number of hospitalizations (for any cause) during the study period was 232 in patients receiving hydroxyurea and 324 in those on placebo. The hospital LOS was not different between hydroxyurea and placebo subjects; hospitalizations on hydroxyurea lasted a mean of 3.7 days (median 3, range 1–9 days) and on placebo a mean of 3.6 days (median 3, range 1–13 days).

The estimated mean inpatient costs for patients in the hydroxyurea and placebo groups for the 6 categories calculated from the regression coefficients in the generalized linear model (Supplemental Table 4) evaluated at specified covariate levels ranged from \$6120 to \$47 199 per hospitalization (Table 1). After multiplying by the number of events in each category and summing the categories, the total inpatient cost for the hydroxyurea subjects was ~\$1 332 000 and for those in the placebo group \$1 992 000. When

these totals were divided by the number of hospitalizations in the 2 groups (173 and 253, respectively), the cost per event was \$7699 in the hydroxyurea group and \$7874 in the placebo group (Table 2). Extrapolating these results over the full period of the study gave an estimated total cost of all hospitalizations of \$1 786 000 for the hydroxyurea group and \$2 551 000 for the placebo group. Dividing by the number of patient-years in each group (189 and 186, respectively) produced an estimated hospitalization cost per patient-year of \$9450 in the hydroxyurea group and \$13 716 in the placebo group (Table 2).

Outpatient Costs

On the basis of MarketScan outpatient claims data for the cost of each service or item in 2009, the outpatient cost per hydroxyurea patient and the hypothetical outpatient cost for a patient with HbSS who was receiving standard care alone over the 2-year period between age 1 year and 3 years was \$3244 for hydroxyurea and \$492 for standard care (annual costs of \$1622 and \$246, respectively; Table 3).

Total Costs

Adding the inpatient and outpatient estimated annual costs for 1- to 3-year-old children with sickle cell anemia together gave totals of \$11 072 (\$9450+1622) for children on hydroxyurea and \$13 962 (\$13 716+246) for those on

placebo. This absolute difference of \$2890 in annual health care costs represented a 21% lower annual cost ($P = .038$) for patients on hydroxyurea when compared with placebo.

DISCUSSION

The BABY HUG study demonstrated clinical benefits of hydroxyurea for infants and toddlers with sickle cell anemia, who had less frequent episodes of pain, dactylitis, and ACS and fewer HSN and TX compared with those receiving placebo. In this retrospective analysis, we found that hydroxyurea treatment was associated with an estimated annual per patient expenditure of ~21% less than estimated for standard care alone. This occurred because inpatient care savings more than compensated for greater outpatient care expenses resulting from additional clinic visits and laboratory monitoring and the cost of hydroxyurea itself. The difference in the annual cost for 1- to 3-year-old children receiving placebo (\$13 962) and those receiving hydroxyurea (\$11 072) was \$2890, which was statistically significant.

The estimated reduction in average cost among children with sickle cell anemia receiving hydroxyurea in this randomized trial was similar to that seen in the only other direct comparison of patients receiving hydroxyurea and those receiving placebo, the retrospective analysis of cost estimates from the MSH trial involving adult

TABLE 1 Inpatient Cost Estimates

Event	Hydroxyurea Group				Placebo Group			
	Average LOS (d)	Cost ^a per HSN (\$)	N ^b	Approximate Cost (\$)	Average LOS (d)	Cost ^a per HSN (\$)	N ^b	Approximate Cost (\$)
HSN	3.6	6419	140	899 000	3.4	6120	192	1 175 000
HSN + TX	3.9	10 734	19	204 000	4.3	11 809	31	366 000
HSN + ACS	4.3	9875	3	30 000	3.7	8557	12	103 000
HSN + ACS + TX	9.0	47 199	1	47 000	5.9	22 520	11	248 000
HSN + SpS	—	—	0	0	3.0	8641	1	9000
HSN + SpS + TX	3.5	15 171	10	152 000	3.5	15 171	6	91 000
Total			173	1 332 000			253	1 992 000

^a Based on MarketScan inpatient claims data for HbSS, age 1 to 3 y, 2009.

^b Number of events that occurred between February 2006 and September 2009 (end of study) = 77% of total number of events.

patients with severe sickle cell anemia, in which the annual total mean expenditure was 30% lower for those assigned to hydroxyurea than for those in the placebo group.⁹

Three other studies have examined the effects of hydroxyurea on the use and costs of medical services based on administrative data. In a review of discharge data from hospitals in Maryland from 1995 through 2003, hospitalization rates for adults with sickle cell anemia increased significantly after US Food and Drug Administration approval of hydroxyurea for severely affected adults in 1998, and inpatient costs increased above the rate of inflation.¹⁰ However, those increases may have reflected increased numbers of adults with sickle cell anemia accessing care and do not shed light on per-person use or costs of inpatient care associated with the introduction of hydroxyurea.

TABLE 2 Overall Inpatient Cost Estimates

Item	Hydroxyurea	Placebo
Cost per HSN event	\$7699	\$7874
Total HSNs (all causes, entire study)	232	324
Estimated total cost of all HSN	\$1 786 000	\$2 551 000
Number of patient-years	189	186
Estimated HSN cost/patient-year	\$9450	\$13 716

TABLE 3 Outpatient Cost Estimates

Item	Hydroxyurea ^a	SC ^b	Cost ^c (\$)	Cost per Patient (\$)	
				Hydroxyurea	SC
Clinic visit	24	7	37	912	259
CBC	24	7	14	336	98
Reticulocyte count	24	7	7	168	49
Chemistry panel	12	2	35	420	70
HbF	4	1	16	64	16
Hydroxyurea drug	24	0	57 ^d	1368	0
Total cost/patient				\$3244	\$492
Cost/patient-year				\$1622	\$246

CBC, complete blood count; SC, standard care.

^a Number of occurrences over the age range of 1.0 to 3.0 y from BABY HUG Study.

^b Number of occurrences if subjects on the placebo arm were receiving "standard care" over the same 2-year period.

^c Based on MarketScan outpatient claims data for HbSS, ages 1 to 3 y, 2009.

^d Based on survey of 4 institutions (see Methods).

Two studies specifically examined costs associated with pediatric use of hydroxyurea. One analyzed data on Medicaid enrollees with sickle cell disease in North Carolina over the period 2000–2008 and identified subjects with filled hydroxyurea prescriptions.¹¹ On the basis of these data, 35% of subjects met the definition of being adherent with taking the drug, and for them, adherence was associated with a reduction in total health care costs of \$6529 ($P < .001$). Another study examined the cost and effectiveness of hydroxyurea in reducing the frequency of pain episodes and hospitalization in pediatric sickle cell disease in South Carolina.¹² Analysis of that state's Medicaid records indicated that those receiving the drug had a higher risk of experiencing vaso-occlusive pain episodes and ACS, as well as significantly higher medical costs than those children not receiving hydroxyurea, which was attributed to the hydroxyurea users having greater severity of disease. However, among those receiving hydroxyurea, average costs fell 31% from \$12 842 to \$8839 ($P < .001$) during the 2-3 year period of active treatment.

In our analysis the reduction in costs in the hydroxyurea group compared with the placebo group was dampened by the fact that all hospitalizations were counted even though many were un-

related to hydroxyurea. There was a 48% lower incidence of hospitalization associated with diagnoses of pain or ACS in the hydroxyurea arm of the trial compared with the placebo arm but only an 11% lower incidence of all other hospitalizations.¹⁸ Thus, the percent reduction in hospitalization costs does not solely reflect the effectiveness of hydroxyurea in preventing hospitalizations for vaso-occlusive complications. Another limitation was that ED data were not analyzed separately; thus patients who had only ED management (without hospitalization) were not included in the comparison. If ED visits for pain occurred more frequently among placebo patients than in those receiving hydroxyurea, the cost differential between the 2 groups again would be understated in the analysis.

In our analysis, there was a lack of data for the specific expenses of the subjects participating in the BABY HUG study. However, it is standard practice for cost-effectiveness analyses to use unit costs taken from other sources in combination with records on numbers of services used.¹⁹ In addition, the use of Medicaid expenditure data may have understated costs of care; based on previous analyses of the MarketScan Multi-State Medicaid and Commercial Claims and Encounters Research Databases, costs for children with sickle cell disease on Medicaid may be ~25% less than those with private insurance.^{15,16} Although the MarketScan database does not identify the 12 states contributing data, those data may be more generalizable at the national level than cost estimates from individual states used in previous cost studies.^{11,12,20} Of note, the claims data used to estimate hospitalization costs lacked sociodemographic information except for age (which was controlled in this analysis by restriction to 1- to 3-year-old children), gender, and, to a limited

extent, race/ethnicity.¹⁴ Another limitation of those data are the use of ICD-9 billing codes to identify children with sickle cell anemia; previous analyses of these data have found that the overall frequency of sickle cell disease among children reported to be black or African American is accurate but that information on subtypes of sickle cell disease is often lacking or imprecisely reported.¹⁶

A full cost-effectiveness analysis of hydroxyurea still needs to be conducted from the societal perspective. Such an analysis would include estimates of the costs incurred by family members in seeking care and in ensuring that a child receives the medication every day. It is likely that including those costs would increase the estimates of cost savings. Although there are costs to families associated with additional outpatient encounters, it is probable that those would be more than offset by the reduction in number of hospitalizations. The travel costs and lost earnings incurred by families whose

child is hospitalized are likely to be substantially greater than the costs associated with outpatient visits because the latter can be anticipated and at least partially accommodated. A societal cost-effectiveness analysis would also need to consider adjusting the Medicaid expenditures used in the present analysis to include estimates of expenditures by private payers, which may better reflect actual resource costs incurred by hospitals. That adjustment would raise the absolute estimate of cost savings from hydroxyurea compared with the findings reported here. Finally, a societal cost-effectiveness analysis would also need to factor in estimates of rates of adherence to provide realistic estimates of effectiveness and costs, which might lower the estimate of cost savings.

CONCLUSIONS

We conclude that the use of hydroxyurea treatment is associated with

substantial medical cost savings, even in very young children with sickle cell anemia and a full spectrum of disease severity. Such savings should become even more pronounced in patients who are >3 years because of the greater frequency of hospitalization for vaso-occlusive events in older children.²⁰ In addition to the beneficial clinical and hematologic effects of hydroxyurea, its limited acute toxicity,⁸ and its relative ease of administration, we believe that the economic benefits from this treatment support the case for offering hydroxyurea to all children with sickle cell anemia, commencing at a young age.

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This trial has been registered at www.clinicaltrials.gov (identifier NCT00006400).

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