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Hydroxyurea Use in Children with Sickle Cell Disease: Do Severely Affected Patients Use It and Does It Impact Hospitalization Outcomes?

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Abstract

Background—Expert guidelines recommend that hydroxyurea (HU) be offered to all children with Hemoglobin SS and $S\beta^0$ sickle cell disease (SCD) and be considered for children with clinically severe Hemoglobin SC or $S\beta^+$. This study aims to determine the rate of HU use in hospitalized children, if HU is differentially used in children with clinically severe SCD, and if HU users have shorter lengths of stay (LOS), fewer intensive care unit (ICU) admissions, and fewer inpatient transfusions compared to non-users.

Procedure—Using the Pediatric Health Information System, we performed a retrospective analysis of children ages 2–18 years with SCD discharged between January 1, 2011–September 30, 2014. We defined patients as having clinically severe SCD if they had a recent ICU admission or ≥3 admissions in the preceding year.

Results—Of the 2,665 unique children identified, approximately 80% had an inpatient code indicating HU use. Significantly more ($p<0.001$) non-users (30.1%) had a recent ICU admission compared to HU users (18.7%). More non-users (33.9%) had a history of ≥3 admissions compared to HU users (21.5%) ($p<0.001$). After applying propensity score weighting, the groups did not differ in their LOS, prevalence of ICU admissions, or prevalence of transfusions.

Conclusion—HU use is high among hospitalized children with SCD. However, HU is not utilized by many children with clinically severe SCD. These results support that HU be considered in children with SCD to prevent hospitalization rather than as a treatment to improve hospitalization outcomes.

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Conflicts of Interest

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INTRODUCTION

Hydroxyurea (HU) is the only disease modifying medication available for children with sickle cell disease (SCD). Multiple clinical trials show that HU reduces vaso-occlusive pain, acute chest syndrome (ACS) episodes, hospitalizations, and erythrocyte transfusions in pediatric patients.[1–3] Retrospective data also suggest that HU reduces mortality in children with SCD because it results in fewer deaths from ACS episodes and infection.[4] These findings led to the 2014 National Heart, Lung, and Blood Institute Expert Panel Report's recommendation that HU be offered to all children with Hemoglobin SS and $S\beta^0$ sickle cell disease (SCD) and be considered for children with Hemoglobin SC and $S\beta^+$ SCD who have clinically severe SCD.[5]

Epidemiology data show that since HU's Food and Drug Administration approval in 1998, hospitalization lengths of stay (LOS) for all children and adults with SCD are significantly shorter, [6] but HU's impact on hospitalized children is unknown. A cost analysis from the BABYHUG clinical trial showed that children who took HU had reduced inpatient costs compared to children taking placebo, but it was unclear if this was because HU prevented hospitalizations or because it reduced the severity of inpatient illnesses.[7] Describing current HU use among hospitalized children with SCD could identify whether HU is being prescribed to children who may benefit from it and whether HU improves hospitalization outcomes.

In this study we aim to determine the current rate of HU use in hospitalized children and to determine if HU is differentially used in children with clinically severe SCD. Additionally, we will examine if hospitalized HU users have improved hospitalization outcomes as measured by fewer deaths, shorter lengths of stay (LOS), fewer intensive care unit (ICU) admissions, and fewer erythrocyte transfusions compared to HU non-users.

METHODS

Study Design and Database

We performed a retrospective analysis of the Pediatric Health Information System (PHIS) inpatient data, a database developed by the Children's Hospital Association. PHIS contains comprehensive clinical and financial data submitted from over 48 Children's Hospital Association member hospitals. Participating PHIS hospitals are among the largest and most advanced children's hospitals in America. Data within PHIS undergo reliability and validity checks prior to inclusion into the database. Patients are de-identified but are coded with unique medical identification numbers to allow individual patients to be followed over time. Nationwide Children's Hospital Institutional Review Board granted exempt status to our use of de-identified data and a PHIS external release was obtained.

Population

Children ages 2–18 years with SCD discharged between January 1, 2011–September 30, 2014 from the 42 hospitals within PHIS that provided complete clinical and financial data were included in the analyses. Only patients' most recent hospitalization during the study period was analyzed to reflect the current rate of HU use. Since children with SCD with an

acute stroke typically require prolonged hospitalizations, ICU admission, receive erythrocyte transfusion and because HU is not a proven therapy for stroke prevention,[8] we excluded admissions that contained an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis for stroke (434.00–434.11, 434.90, 434.91, 438).

Data Collection

The following patient data within PHIS were obtained for all eligible discharges: age, gender, HU use, discharge status (dead, alive), ICU admission, asthma diagnosis, total number of ICD-9-CM diagnoses, LOS (days), erythrocyte transfusion, and insurance provider (private, public, unknown). We considered patients to be HU users if their hospitalization data contained the Pharmacy Current Procedural Terminology code for HU (171927). Since the ICD-9-CM codes for SCD genotype are not discreet, we did not use SCD genotype in our analyses. Instead, we defined patients as having clinically severe SCD if they had a history of a recent ICU admission (after 2009) or a history of ≥3 hospital admissions in the year preceding their most recent admission. This severity definition was selected because it is used in clinical practice and in clinical trials [3,9] to identify children with severe SCD and because it could be captured within PHIS.

Statistical Analyses

Descriptive statistics were used for independent variables in our study cohort. For continuous variables (age, number of diagnoses) we performed t-tests. We used Chi-Square tests to compare categorical variables (gender, asthma diagnosis, ICU history, inpatient admission history, and insurance) across exposure categories (HU users and non-users). T-tests and Chi-Squared tests were performed before and after applying propensity score weighting.

Propensity scores can be used to reduce bias in observational studies when the baseline characteristics of the study groups that are being compared are different.[10, 11] Propensity score weighting is a statistical method that can be applied when the baseline covariates between groups are not balanced. Propensity score weighting was used instead of matching to avoid discarding HU users' hospitalization data. In this study, weights in the HU-user group were defined as (1/probability of being in the HU-user group) and as (1/probability of being in the non-user group) for the non-user group. Patient age, gender, co-existent asthma diagnosis, recent ICU admission, total number of ICD-9-CM diagnoses for analyzed admission, three or more admissions in the prior year, and primary insurance were included in the propensity weights. Three outcomes were used to compare HU users and non-users after applying propensity weights: (1) a Poisson regression to model the average LOS, (2) a logistic regression to model the prevalence of being admitted to the ICU, and (3) a logistic regression to model the prevalence of being given an erythrocyte transfusion. The "Treatment Effects" program was implemented using Stata, version 14.0 (StataCorp®, LP). This program simultaneously estimates propensity scores and the outcome model.

RESULTS

Clinical Characteristics

We identified 2,665 unique children with SCD, after excluding one HU user with missing gender information. Approximately 80% of the children had an inpatient code indicating that they were prescribed HU during their admission. Most of the study cohort was coded as having Hemoglobin SS SCD (Table I). Six patients died during hospitalization, two HU users and four non-users.

HU users differed in their baseline characteristics compared to non-users. After propensity score weighting balanced these covariates, HU users and non-users were similar across all covariates (Table II).

Severity of Illness

Admission to the ICU—During the study period, 146 (5.5%) patients required care in the ICU. After applying propensity weighting, HU users had a 1.3% higher prevalence of being admitted to the ICU compared to non-users (95% CI: −0.0034, 0.0289), but this difference was not statistically significant.

Erythrocyte transfusion—In the entire cohort, 668 (25.1%) of the patients received at least one erythrocyte transfusion. After applying propensity weighting, there was a 1.9% lower prevalence of receiving an erythrocyte transfusion among HU users (95% CI: −0.0628, 0.253) compared to non-users, but this difference was not statistically significant.

LOS—The average LOS for the entire cohort was 4.23 days (SD ± 7.18 days). After propensity weighting, HU users had a longer average LOS (4.01 days, 95% CI: 3.8404, 4.1721) compared to non-users (4.18 days, 95% CI: 3.6985, 4.6663), but this difference was not statistically significant.

DISCUSSION

Our study confirms that HU use is high among hospitalized children with SCD. Interestingly, we found that 30% of patients with a recent ICU admission and 33% of patients with a history of at least 3 admissions did not use HU, despite few other available disease modifying therapies. It is possible that some non-users were receiving chronic transfusion therapy instead of HU to treat their SCD, but we suspect that this occurred in only a few patients, since patients with a history of stroke, one of the common indications for chronic transfusion therapy, were excluded. Furthermore, we queried a subset of PHIS data and identified that <5% of HU non-users meeting our eligibility criteria received ≥7 transfusions during the study period. This suggests that HU may be worth stronger consideration in children with clinically severe SCD, as HU is proven to prevent hospitalization in children with clinically severe SCD [3,9] and because hospitalization is a risk factor for developing other complications, such as ACS.[12]

There is increasing interest in exploring HU's anti-inflammatory properties and then using HU as an anti-inflammatory agent in the acute setting for patients with SCD.[13] Our results

suggest that HU use does not significantly impact the severity of illness in hospitalized children. This may be because HU's primary mechanism of action is to induce fetal hemoglobin production [2] and this process can take many months to prevent vaso-occlusive pain and ACS episodes.[14] Further investigation is needed to determine if increased HU dosing or intravenous HU administration may be able to achieve an anti-inflammatory effect that is sufficient to result in improved hospitalization outcomes.[15] Currently, erythrocyte transfusion remains the only therapy available that rapidly reduces the percentage of sickled erythrocytes to impact the severity of illness in hospitalized patients.[16,17] Since supportive care interventions (e.g. incentive spirometry) reduce secondary complications in hospitalized patients that result in longer LOS,[18,19] interventions that optimize these supportive care therapies may also be another way to reduce LOS, ICU admissions, and erythrocyte transfusions in children with SCD until novel interventions are developed and tested.

A limitation of our study is the potential for coding errors,[20] since PHIS uses ICD-9-CM and other billing codes to identify outcomes in hospitalized patients. We specifically did not use patients' coded SCD genotype in our propensity score weighting. The ability of these codes to accurately identify patients' SCD genotype or disease severity is not known, but likely unreliable, because the ICD-9-CM codes for the SCD genotypes are not discreet and inappropriately group patients together. For example, the ICD-9-CM codes for Hemoglobin S-β Thalassemia (282.41, 282.42) do not distinguish between Hemoglobin $S\beta^+$ and Hemoglobin $S\beta^0$ SCD, even though patients with Hemoglobin $S\beta^0$ SCD have more severe SCD than patients with Hemoglobin $S\beta^+$.[4] To limit these potential errors from impacting our comparisons, we used variables that have more straightforward ICD-9-CM coding. It is also important to note that we were not able to determine if patients may have initiated HU during their hospitalization or if some patients may have had their HU held or mistakenly not ordered during their entire hospitalization. Since HU is not a proven treatment from complications in the acute setting and because 80% of the cohort was prescribed HU at some point during their hospitalization, we suspect that HU was not frequently initiated or held completely during patients' hospitalizations.

We also note there are few limitations when applying propensity score weighting. First, it does not eliminate the potential for unmeasured confounding. Second, it assumes that there is a constant treatment effect over the course of the study.[21] Since PHIS does not contain information about patients' HU dose, adherence, duration of therapy, or hematologic response and because these are all potential factors that may modify HU's effect on patients over time, we were unable to evaluate if HU had a constant effect.[9,22,23]

In summary, we report that hospitalized children with SCD frequently use HU. However, HU is not utilized by many children with clinically severe SCD who have limited other treatment options. Our results support consideration of HU in children with SCD to prevent their hospitalization, rather than as a treatment to improve their hospitalization outcomes. To improve the care of hospitalized children with SCD, additional treatments are needed to reduce their LOS, ICU admissions, and need for erythrocyte transfusions.

Abbreviations

HU	Hydroxyurea
SCD	Sickle cell disease
LOS	Length of stay
ICU	Intensive care unit
ACS	Acute chest syndrome
PHIS	Pediatric Health Information System
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification

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Table I

Patients' HU Use By ICD-9-CM Coded SCD Genotype

SCD Genotype	ICD-9-CM Codes	Patients n=2,665 (% of total patients)	HU-Users n=2,166 (% of genotype)	Non-Users n=499 (% of genotype)
SS	282.61 282.62	2,225 (83.5)	1,820 (81.8)	405 (18.2)
Sβ Thalassemia	282.41 282.42	190 (7.1)	160 (84.2)	30 (15.8)
SC	282.63 282.64	116 (4.4)	76 (65.5)	40 (34.5)
Unspecified	282.60, 282.68, 282.69	134 (5.0)	110 (82.1)	24 (17.9)

Table II

Baseline Characteristics of HU Users and Non-Users Before and After Propensity Score Weighting

	Before Weighting*		p value	After Weighting		p value
	HU Users n=2,166	Non-Users n=499		HU Users n=2,664	Non-Users n=2,672	
Age (mean, SD)	11.12 (4.75)	11.72 (4.75)	0.013	11.23 (5.27)	11.13 (11.86)	0.704
Gender (n, %)						
Male	1,140 (52.6)	244 (48.9)	0.132	1,384 (52.0)	1,391 (52.1)	0.970
Female	1,026 (47.4)	255 (51.1)		1280 (48.0)	1,281 (47.9)	
Asthma Diagnosis (n, %)	746 (34.4)	186 (37.3)	0.232	932 (35.0)	938 (35.1)	0.961
Number of Diagnoses (mean, SD)	5.64 (3.33)	6.84 (5.13)	<0.001	5.84 (4.26)	5.76 (8.11)	0.673
Recent ICU Admission (n, %)	404 (18.7)	150 (30.1)	<0.001	533 (20.2)	559 (20.9)	0.935
≥3 Admissions in Prior Year (n, %)	465 (21.5)	169 (33.9)	<0.001	634 (23.8)	641 (24.0)	0.921
Insurance (n, %)						
Private	561 (25.9)	115 (23.1)	0.081	673 (25.3)	663 (24.8)	0.973
Public	1,546 (71.4)	359 (71.9)		1,906 (71.6)	1,923 (72.0)	
Other/Unknown	59 (2.7)	25 (5.0)		84 (3.1)	86 (3.2)	

* One patient with unknown gender (a HU user) was excluded from the analysis.