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Effectiveness of Hydroxyurea in the Management of Sickle Cell Disease

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MBChB, University of Ghana, 2004

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An abstract of

A thesis submitted to the Faculty of the

James T. Laney School of Graduate Studies of Emory University

in partial fulfillment of the requirements for the degree of

Master of Science

in Clinical Research

2014

Abstract

Effectiveness of Hydroxyurea in the Management of Sickle Cell Disease

By Maa-Ohui Quarmyne

Background: The clinical efficacy of hydroxyurea (HU) in sickle cell anemia (SCA) has been established over the last two decades. HU has been demonstrated to improve hemoglobin levels and to decrease hospitalizations, episodes of pain, acute chest syndrome and mortality. While evidence supporting its efficacy is well demonstrated, published data about its effectiveness in clinical practice is limited. This study sought to evaluate the clinical effectiveness of HU in a large pediatric sickle cell population using a pre-post study design to control for disease severity selection bias.

Methods: Outcomes of patients with SCA (SS/SBeta Zero Thalassemia) who initiated HU in 2009-2010 at Children's Healthcare of Atlanta (CHOA) were studied in a retrospective, pre-post cohort design. Patients with overlapping chronic transfusions, multiple hydroxyurea start dates, and lack of follow up data were excluded. For each patient, events during the 2-year prior to initiation of HU were compared to the 2 years after initiation. Univariate analysis was performed using paired T tests and Wilcoxon Signed Rank Test. Multivariable modeling using Poisson regression was performed to evaluate the interaction between effect of hydroxyurea and age, sex and insurance status (α=0.05).

Results: Of 1,111 patients with SCA who received care at CHOA, 127 patients started hydroxyurea during 2009-2010, and 91 met eligibility criteria. During the 2-year period after initiation of hydroxyurea, there was a significant decrease in hospitalizations, ER visits and pain encounters. Rates of pain encounters, hospitalizations and ER visits after hydroxyurea initiation were 0.61 ($p < 0.0001$), 0.64 ($p=0.0005$) and 0.68 ($p= 0.0001$) times compared to the rates before, respectively. Average hemoglobin levels improved by 0.67g/dl ($p<0.0001$). The effect of HU on hospitalizations was modified by age with the younger children (<10years) having the greatest decrease in hospitalizations (Rate Ratio 0.46 vs. 1). There was no interaction between the effect of hydroxyurea and sex or insurance status.

Conclusions: HU is clinically effective in the children with SCD. HU decreased hospitalizations, pain encounters and ED visits and improved hemoglobin levels. The effectiveness of HU is strongest when HU is initiated at younger ages.

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Acknowledgements

I am grateful to my clinical mentors, Clinton Joiner, Peter Lane and Clark Brown for their guidance and mentorship with this project. I am also grateful to my thesis readers, Mitch Klein and Matthew Magee, and the professors in the MSCR program for their guidance with this project. Rodney Theodore, Christopher Perry and Yuritzi Jones were also of immense help in compiling the data for this study. The Children's Healthcare of Atlanta Outcomes Center staff namely, Wei Dong, James Bost, Greg Rocks and Brad Kloth also provided countless hours of assistance in data generation and statistical guidance for which I am truly grateful.

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A. INTRODUCTION

Sickle cell disease (SCD) is a group of multi-system, life-threatening blood disorders which affects 100,000 people in the US and millions of people worldwide(1, 2). SCD is characterized by acute and chronic pain, chronic anemia, increased susceptibility to infections, central nervous system vasculopathy including stroke, and end organ damage affecting the kidneys, lungs, liver, reproductive organs and eyes(3). However, there is marked inter-individual and temporal variability in the clinical presentation of the disease.

Newborn screening for SCD, prophylactic penicillin treatment and comprehensive specialized care have resulted in improved outcomes for children with sickle cell disease, especially in developed countries(4-6). Nevertheless, patients affected by the disease have significant morbidity and early adult mortality(7, 8).

A number of disease modifying therapies are currently clinically available in sickle cell disease, namely hydroxyurea, blood transfusions and bone marrow transplant. Bone marrow transplantation is curative in SCD but its use has been limited by its lack of availability to the large majority of patients with the disease, as well as concerns about transplant related mortality and long-term adverse effects (9-12). Chronic transfusions are particularly known to decrease the rates of stroke in SCD(13-15), but are associated with significant toxicities including iron overload and risk for allo-immunization to minor red cell antigens. In addition, this therapy is currently not feasible in less developed countries where the large majority of patients with sickle cell disease reside and where there is persistent shortage of blood supply. Hydroxyurea is currently the only disease-modifying drug for SCD approved by Food and Drug Administration (FDA). Hydroxyurea has been well demonstrated in clinical trials to alter the clinical course in SCD. It improves hemoglobin levels and decreases the need for transfusions. It also decreases

rates of pain, dactylitis, episodes of acute chest syndrome (ACS) and hospitalizations(16, 17). Other clinical studies have shown that hydroxyurea improves quality of life and decreases mortality(18-21).

Thus hydroxyurea is currently the only disease modifying therapy with the potential to be used worldwide, in both developed and developing countries, to improve outcomes in sickle cell disease. While data on the efficacy of hydroxyurea has been well demonstrated, data on its effectiveness is limited. A 2008 National Institutes of Health (NIH) consensus statement on hydroxyurea use in sickle cell disease identified future research studies on the effectiveness and cost effectiveness of hydroxyurea in the sickle cell population as a research need due to the prevailing lack of information in this area(22).

The goal of this study was thus to establish the effectiveness of hydroxyurea in the country's largest pediatric sickle cell disease program in a retrospective cohort study using a pre-post treatment approach. The **hypothesis** was that hydroxyurea is effective in sickle cell disease, specifically that in a 2 year period after its initiation, compared with the preceding 2 years, hydroxyurea decreases

- Frequency of hospitalizations and total inpatient days
- Cost of care
- Sickle cell associated complications

We also posited that the effect of hydroxyurea would be modified by age, sex and insurance status.

B. BACKGROUND

SCD is caused by a point mutation in the beta globin gene that produces mutant hemoglobin S (HbS) with a single amino acid substitution ($\beta 6^{glu \rightarrow val}$). Individuals with SCD, are homozygous for HbS or inherit HbS and one other abnormal beta globin gene. In the US and in populations of African descent, homozygous SS (HbSS) is the commonest form of sickle cell disease(2, 23). Other genotypes include HbSC, HbS Beta Plus ($HbS\beta^{+}$) thalassemia HbS Beta Zero ($HbS\beta^{0}$) thalassemia. The fundamental basis of SCD pathophysiology results from abnormal polymerization of deoxygenated HbS, leading to occlusion of blood vessels that results in pain episodes, a hallmark of SCD, as well as chronic organ damage which is ultimately responsible for the early demise of most SCD patients. This pathology is exacerbated by pronounced humoral and cellular inflammation, activation of both coagulation and fibrinolysis, and marked endothelial cell activation and dysfunction. In addition, the hemolytic component of SCD, results in free hemoglobin and heme in plasma, important contributors to these pathologies (3, 24, 25).

Hydroxyurea, currently the only FDA approved treatment for patients with sickle cell disease, induces the production of fetal hemoglobin (HbF), which inhibits the polymerization of HbS and thus decreases vaso-occlusion and hemolysis. Additional beneficial effects of hydroxyurea include decrease in the numbers of white blood cells and reticulocytes and improved rheology of red blood cells, all of which result in decreased vaso-occlusion, improved blood flow, decreased red cell hemolysis and improved anemia(26). These physiological effects of hydroxyurea have been associated with decreased frequency of pain episodes, need for transfusions, frequency of acute chest syndrome, cost of care, improved quality of life, and ultimately, decreased mortality both in children and adults with the disease (16, 17, 19-21, 27-30). In a double blind randomized, placebo-controlled trial of about 300 adults with sickle cell disease, Charache et al demonstrated after a follow up period of 21 months that hydroxyurea lowered annual rates of pain crises

(median, 2.5 vs. 4.5 crises per year, P value <0.001), decreased the number of episodes of acute chest syndrome (25 vs. 51, P value <0.001) and the need for transfusions (48 vs. 73, P value=0.001)(16). In another 17-year prospective study, Voskaridou et al demonstrated a dramatic reduction in the frequency of severe painful crises, transfusion requirements, hospital admissions and incidence of acute chest syndrome in adults on hydroxyurea. The probability of a 10-year survival of patients on hydroxyurea in this cohort was 86%, compared to 65% in patients not on hydroxyurea even though patients on hydroxyurea had more severe forms sickle cell disease(21). Similarly, in a randomized controlled trial in very young children with sickle cell disease, hydroxyurea was shown to decrease pain episodes (hazard ratio 0.59, p value = 0.002), hospitalization rates (hazard ratio 0.73, p value = 0.05), acute chest syndrome (hazard ratio 0.36, p value = 0.02), and need for transfusions (hazard ratio 0.55, p value = 0.03)(17).

Nevertheless, hydroxyurea remains underutilized. Using NIH guidelines for administration of hydroxyurea, Lanzron et al found that only 70% of hospitalized adult patients who were eligible for hydroxyurea were on the medication(31). A number of provider, caregiver and patient barriers to the use of hydroxyurea have been identified and these include lack of adequate knowledge about the drug, doubts about the drug's effectiveness, concerns about side effects and compliance (32-34).

While the efficacy of hydroxyurea has been well demonstrated in several clinical trials, information about its effectiveness remains limited. Efficacy examines the therapeutic effect of an intervention in a controlled setting, in contrast to effectiveness, which is the therapeutic effect of an intervention in real-world situations. Attempts to compare the clinical effectiveness of hydroxyurea have been limited by a number of reasons including inherent selection bias for disease severity in patients on hydroxyurea (35). A 2008 National Institutes of Health (NIH) statement on hydroxyurea stated; 'The efficacy of hydroxyurea in treating adults with sickle cell

disease is established. Data on the effectiveness of hydroxyurea are limited, but the experience of multiple physicians and clinics strongly suggests that the drug is highly effective in widespread practice'. Due to the prevailing lack of information in this area, the consensus statement (22) identified the need for future research studies on the effectiveness and cost effectiveness of hydroxyurea in the sickle cell population.

This study was designed to address that need and provide additional information about the effectiveness of hydroxyurea in clinical practice. The unique advantages of this pre-post study design and use of the CHOA sickle cell disease dataset include:

- Relatively large pediatric population of patients with sickle cell disease. CHOA provides care to over 1700 children with SCD, making it the largest pediatric program in the country.
- Confirmed diagnosis of type sickle cell disease by pediatric hematologists via review of medical records and laboratory results. This provides additional diagnostic accuracy and reliable data as compared to use of ICD codes and administrative datasets, which are fraught with inaccuracies.
- Access to healthcare utilization data, associated diagnosis and complications, insurance and healthcare charges for pediatric patients with sickle cell disease in the Atlanta Metropolitan area. CHOA provides care to about 95% of pediatric patients with sickle cell disease in the Atlanta Metropolitan area, providing a sample that is representative of a population-based sample.

C. METHODS

This retrospective cohort study utilized a pre-post comparison design, with the primary goal of assessing the clinical effectiveness of hydroxyurea in a pediatric population with sickle cell anemia. Data for the study was obtained from the CHOA sickle cell database, medical records and chart review. The CHOA Institutional Review Board approved this study with a waiver of consent from participants.

The CHOA sickle cell database consists of about 1,700 patients with sickle cell disease from three clinical campuses of CHOA (Egleston, Scottish Rite and Hughes Spaulding). Within the 28-county Greater Metropolitan Atlanta Area, these 3 hospitals account for 95% of all inpatient hospitalizations for individuals with SCD < 18 years of age. Thus the information available on the database is representative of a population-based sample. For all patients listed in the database, a pediatric hematologist has confirmed the diagnosis of sickle cell disease by review of laboratory results and clinical notes. Table 1 gives additional descriptive information about the dataset. Information available from this database includes utilization (emergency room visits, inpatient hospitalization, clinic visits), insurance status, socioeconomic status, treatment status and healthcare charges.

Subjects for the study were identified based on the following criteria:

Inclusion criteria:

- Sickle cell anemia (HbSS or HbSβ^0 thalassemia)
- Initiation of hydroxyurea in 2009-2010
- Treatment with hydroxyurea for at least 3 months after initiation

Exclusion criteria

- Other types of sickle cell disease
- Initiation of hydroxyurea outside the stated time period

- Concurrent chronic blood transfusions
- Limited or no follow up data pre- and/or post-hydroxyurea start date. Patients for whom less than 3-month follow up time either pre- or post- hydroxyurea were excluded.
- Unknown hydroxyurea start date

For each subject demographic information, laboratory values, utilization, healthcare charges and outcomes were abstracted for the two-year period prior to the hydroxyurea start date and for an additional 2-year period after their hydroxyurea start date (i.e. a five year period from 2007-2012). The information was abstracted from the CHOA sickle cell database, and from electronic medical records using the information technology query, tool Population Discovery. Additional information was also obtained by individual review of paper and electronic medical records. The CHOA IRB approved this study in June 2013.

To evaluate the effectiveness of hydroxyurea, the following outcome variables were determined for the two years preceding the start of hydroxyurea and for the two subsequent years after the start of hydroxyurea:

i. Number of inpatient hospital days
ii. Number of hospitalizations
iii. Number of emergency room visits
iv. Number of encounters for pain (defined as a visit requiring an parenteral opioid and/or ketorolac).
v. Healthcare charges (inpatient, outpatient, emergency room and total cost)
vi. Hemoglobin level (separate pre- and post-hemoglobin levels were the average of all the hemoglobin values measured over the two year pre- and post- time periods)

The exposure variable of interest was hydroxyurea and the primary outcome variables were number of hospitalizations and inpatient days. Emergency room visits, pain encounters, healthcare charges and hemoglobin levels were analyzed as secondary outcome variables.

Statistical Analysis:
SAS 9.3 was used for data analysis.

I. Initial descriptive statistics of the study population included means (and 95% confidence intervals) and medians (with interquartile range or ranges) for quantitative data, and proportions/frequencies for categorical data.

II. Univariate Analysis

    a. Pre-post analysis of outcome variable (i-vi above) was performed using paired T test and Wilcoxon Signed Rank Test

III. Multivariable Analysis

    a. Poisson regression was performed to assess the effect of hydroxyurea on the primary outcome variables (hospitalizations and inpatient days).

    b. Poisson regression was also performed to assess the interaction between the effect of hydroxyurea and age, sex and insurance status.

IV. Statistical inferences were made based on $\alpha=0.05$

D. RESULTS

Ninety-one (72%) of 127 patients with sickle cell anemia (HbSS and HbSβ^0 thalassemia) who started hydroxyurea in 2009 – 2010 met eligibility criteria and use included in the analysis (Figure 1, 2a and 2b). Four eligible patients were inadvertently excluded during data compilation. The median age of the study population was population was 8 years. Table 2 describes the demographics of the study population.

Initial paired analysis using the Wilcoxon Signed Rank Test showed statistically significant decreases in both primary outcomes variables, the number of hospitalizations and inpatient days for the two-year period after initiation of hydroxyurea compared to the same time period prior to hydroxyurea initiation (Table 3). Tables 4a and 4b compare the change in secondary outcome variables after initiation of hydroxyurea. ED visits and pain encounters decreased on hydroxyurea. Hemoglobin levels improved by an average of about 0.7g/dl ($p<0.0001$). These results are comparable to published efficacy data on hydroxyurea which demonstrate similar findings – improved hemoglobin levels, decreased hospitalizations and pain events (16, 17). There was a significant increase in outpatient charges in the two-year period after initiation of hydroxyurea and a decrease in ED charges. There were however no significant changes in total cost and inpatient cost, though inpatient days and hospitalizations decreased.

Rates of hospitalizations, inpatient days, ED visits and pain encounters were also reduced when evaluated using Poisson regression. The rate ratios (RR) for each of these outcomes were:

- Hospitalizations – RR 0.64 (Confidence Interval 0.49 – 0.82, p value 0.0005)
- Inpatient Days - RR 0.57 (Confidence Interval 0.44 – 0.73, p value 0.0001)
- Pain encounters – RR 0.61 (Confidence Interval 0.48 – 0.78, p value <0.0001)
- ED visits – RR 0.68 (Confidence Interval 0.56 – 0.83, p value 0.0001)

Multivariable modeling using Poisson Regression demonstrated significant interaction between the effect of hydroxyurea and age but there was no interaction between the effect of hydroxyurea and sex, or insurance status. Children $\leq$ 10 years of age had greater than 50% reduction in hospitalizations and inpatient days after initiation of hydroxyurea but no significant differences were seen in children > 10 years of age.

E. DISCUSSION/CONCLUSIONS

The results of this study demonstrate that hydroxyurea is clinically effective in pediatric patients with sickle cell anemia, and that the effect of hydroxyurea is modified by age of initiation. After initiation of hydroxyurea, hospitalization rates and inpatient days decreased by 36% and 43% respectively. In the Baby HUG study, a landmark clinical trial evaluating efficacy of hydroxyurea in children, hospitalizations were marginally reduced in patients on hydroxyurea, compared to placebo (Hazard Ratio 0.73, 95% CI 0.53-1, p value 0.05)(17). Hydroxyurea also had additional beneficial effects on other secondary outcome variables. Inpatient days decreased by 43%, ER visits by 32%, pain encounters by 39% and hemoglobin levels improved by an average of 0.7g/dl. These results are similar to published efficacy results in sickle cell disease. In the Baby Hug study, subjects on hydroxyurea had mean hemoglobin levels 0.9g/dl higher compared to those on placebo at the end of the study period(17) and in the adult MSH study, subjects on hydroxyurea had hemoglobin levels 0.6g/dl higher compared to subjects on placebo(16, 36). The median number of pain events in adult patients on hydroxyurea in the MSH trial, was 44% lower compared with placebo (2.5 vs. 4.5 pain events/yr., $p<0.001$)(16). Similarly, pediatric patients on the Baby Hug study had nearly 40% reduction in pain events (hazard ratio 0.59, 95% CI 0.42-0.83, p value 0.002)(17). Our results are important as they indicate that in 'real life settings', with imperfect compliance and without the incentives for improved compliance as is often the case in clinical trials (i.e. free supply of drugs, reminders for clinic visits, pill counting to measure compliance, financial incentives for follow up visits etc.), hydroxyurea improves outcomes.

As mentioned earlier, the current study also suggests that the effect of hydroxyurea on hospitalizations is affected by age of initiation of the drug with the youngest children having the most benefit. While the rates of hospitalization in older patients were not statistically different

pre- and post- hydroxyurea, Tables 5a suggests a trend of decreased hospitalizations for children in the older age groups. The lack of demonstrable effectiveness of hydroxyurea in older age groups might be due to a number of factors. Older children and teenagers, unlike toddlers, may be less compliant with medications and have less parental oversight of medication administration. Secondly, there were fewer numbers of patients in the older age groups in this study hence a possible lack of power to demonstrate the effect. Lower effectiveness in older children and adolescents is unlikely to be biological, as adults on hydroxyurea in the MSH trial had lower median annual rates of pain compared to patients on placebo thus demonstrating efficacy of hydroxyurea in adults(21). The lack of demonstrable effectiveness in older children and teenagers in this study therefore needs additional evaluation. By measuring laboratory values which are known to change with hydroxyurea administration (such as mean corpuscular volume and hemoglobin F level), and comparing patients with the expected changes in these laboratory values with patients with no significant changes in these values, the effectiveness of hydroxyurea in compliant teenagers may be assessed in future studies.

We evaluated the interaction between the effect of hydroxyurea and insurance status, because insurance status is sometimes used as a surrogate measure of socio-economic status, and found no effect. Thornburg et al also demonstrated in the Baby Hug trial that adherence to study medication was also not affected by socioeconomic status (37). We also found no relationship between effect of hydroxyurea and gender.

Prior studies have demonstrated that hydroxyurea is cost effective (28, 30, 33, 38). Wang et al(30) demonstrated in the Baby HUG study that use of hydroxyurea was associated 21% decrease in annual per patient expenditure compared to standard care. This occurred because inpatient savings more than compensated for the increased outpatient costs incurred from closer outpatient follow up and increased laboratory work. Our data supports this same trend. The

current study showed statistically significant decreases in ED charges and increases in outpatient charges. We also observed a trend toward decreased total charges, though not statistically significant. There were marked variations in inpatient charges in this study with no demonstrable significant change in inpatient charges.

The strengths of this study included the relatively large sample size, which closely estimates a population-based sample of pediatric patients with sickle cell disease. The use of pre-post analysis allows for control of variables that do not change and symmetrical time periods pre- and post-initiation of hydroxyurea allowed for control of varied patterns of hospitalization that may occur with changing seasons in the sickle cell population.

A number of limitations are also acknowledged. Indications for use of hydroxyurea have been evolving rapidly. During the period of the study, hydroxyurea was indicated for patients with more severe clinical phenotypes. The results may therefore not be generalizable to patients with less severe phenotypes, some of whom are now being treated with hydroxyurea. Secondly, subjects for whom hydroxyurea was initially prescribed, but who then discontinued the medication before 3 months were excluded. Thus the study may have selected for patients who are more likely to be adherent. Thus the current study was not an "intention to treat" study that would have included all patients for whom a prescription for hydroxyurea written even if they never started the medication. We also did not capture potential temporal confounders such as use of concomitant medications and other co-existing diseases, that might have been different between the pre- and post hydroxyurea time periods.

In conclusion, our data demonstrate that hydroxyurea is clinically effective in pediatric patients with sickle cell disease. As has been established in control clinical trials, we have demonstrated

that in ‘real world settings’, hydroxyurea reduces hospitalization rates, pain and ED visits. The effect of hydroxyurea depends on age at initiation.

Future Directions:

We hope to explore with additional patients, the effect of age on hydroxyurea effectiveness by expanding the cohort to include other hydroxyurea start dates and also by examining other clinical and laboratory variables which might predict which older children are more likely to respond to hydroxyurea. We will also evaluate the effectiveness of hydroxyurea on other outcomes in sickle cell disease such as acute chest syndrome, use of blood transfusions, and other chronic organ damage. Finally, the clinical effectiveness of other interventions on outcomes in patients with other hemoglobinopathies and thalassemia will be examined.

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G. TABLES/FIGURES

Table 1. Children's Healthcare of Atlanta 2012 Sickle Cell Disease Dataset (n= 1671) – Age, genotype and insurance status.

	N	Percentage (%)
Sex (Female)	840	50.3
Genotypes		
• SS/SB0 thalassemia	1111	66.5
• SC	426	25.5
• SB+ thalassemia	118	7.1
• Other	16	1%
Insurance		
• Medicaid	588	35.2
• Managed Medicaid	378	22.6
• Private Insurance	484	29
• Mixed Insurance	199	11.9
• Self Pay	22	1.3

** Median Age 9 years (interquartile range 5-14)

Figure 1: Treatment Modalities for patients with Sickle Cell Anemia (HbSS and HbSβ^0 Thalassemia) at Children's Healthcare of Atlanta

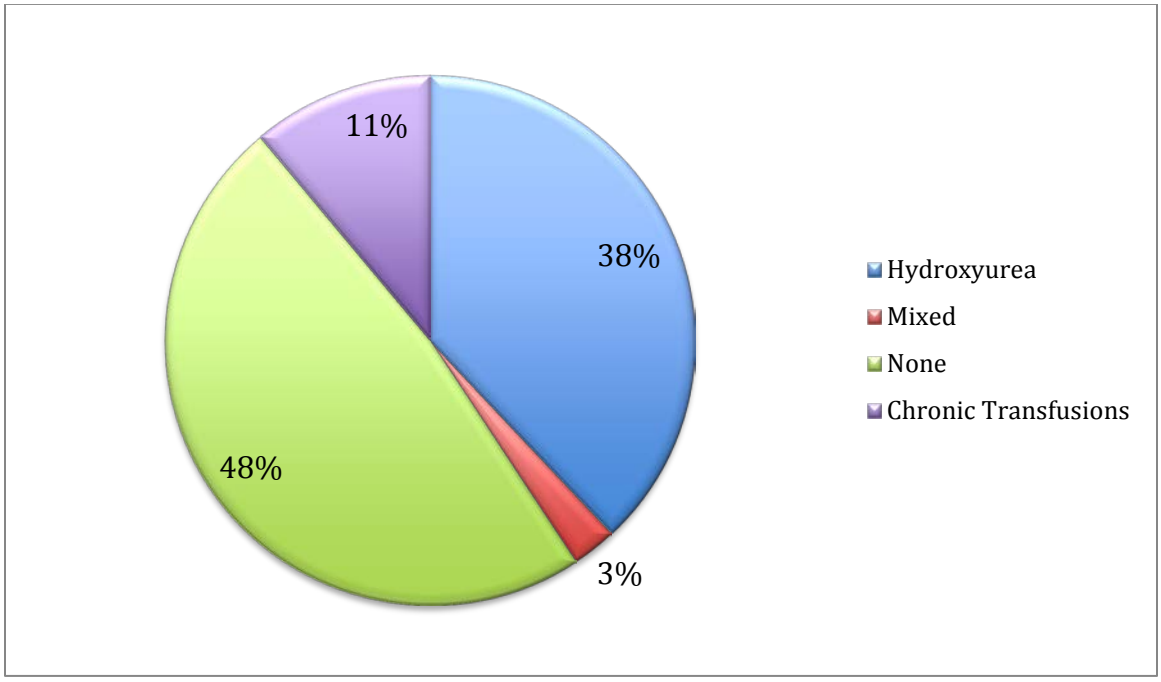

Figure 2a: Selecting the study population from CHOA 2012 Sickle Cell Disease Dataset

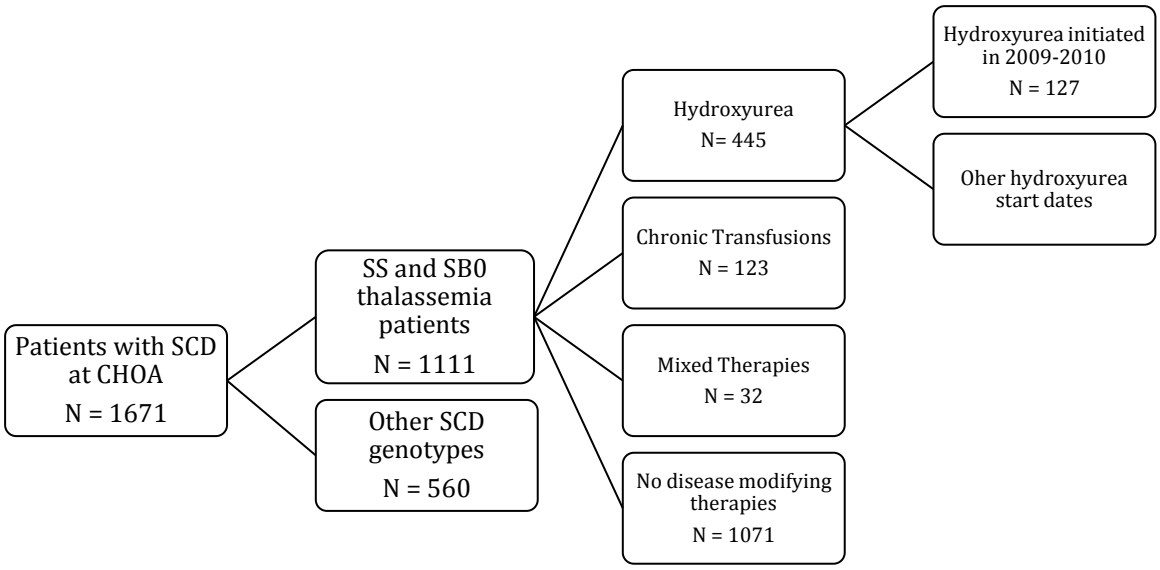

Figure 2b: Selecting Study Patients from patients with HbSS/HbSβ^0 thalassemia who started hydroxyurea in 2009 -2010.

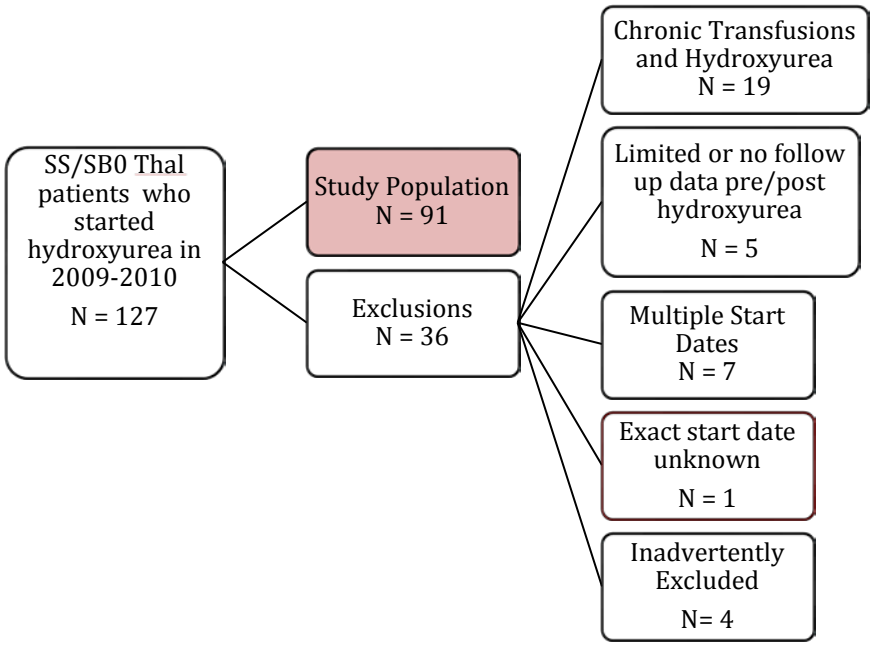

Table 2: Demographic Description of Study Population (2009-2010 Hydroxyurea Treatment Group) – Age, Sex and Insurance (N=91).

	N	Percentage (%)
Sex		
• Male	42	46.1
• Female	49	53.9
Age (years)		
• 0 – 5	32	35.2
• 6 – 10	28	30.8
• 11 -15	20	22.0
• >15	11	12.0
Insurance		
• Medicaid	38	54.0
• Managed Medicaid	9	10.3
• Private Insurance	29	33.3
• Mixed Insurance	11	12.6

** Median Age 8 years (interquartile range 4-14)

Table 3: Comparison of Primary Outcome Variables (Hospitalizations and Inpatient Days) Pre- and Post-Hydroxyurea.

Outcome (N)	Pre - Hydroxyurea Median (IQR)	Post- Hydroxyurea Median (IQR)	Change Median (IQR)	*P value
Hospitalizations	2 (1 – 3)	1 (0 – 2)	- 1 (-2 – 0)	**0.0001***
Inpatient Days	6 (2 – 12)	2 (0 – 8)	- 2 (-8 – 0)	**<0.0001**

* Wilcoxon Signed Rank Test

Table 4a: Comparison of Secondary Outcome Variables (Hemoglobin, ED visits, Pain encounters) Pre- and Post-Hydroxyurea.

Outcome	Pre-Hydroxyurea Median (IQR)	Post-Hydroxyurea Median (IQR)	Change Median IQR	*P Value
Hemoglobin (g/dl)	8.0 (7.5 – 8.6)	8.8 (8.2 – 9.5)	0.7 (0.2 – 1.7)	<0.0001
Pain encounters (N)	2 (1 – 4)	1 (0 – 2)	-1 (-3 – 0)	0.001
ED Visits (N)	4 (2 – 7)	2 (0 – 6)	-1 (-2 – 0)	0.0006

*Wilcoxon Signed Rank Test

Table 4b: Comparison of Secondary Outcome Variables (Cost) Pre- and Post-Hydroxyurea

Cost ($)	Pre-Hydroxyurea Median (range)	Post-Hydroxyurea Median (range)	Change Median (range)	*P Value
Total	48,067 (1,406 - 470,065)	33,415 (1,519 - 372,353)	-2,923 (-453,527 - 176, 633)	0.31
ED	24, 393 (7,280 - 54,622)	7,661 (0 - 301,238)	-4,465 (-153,751 - 150,559)	**0.003**
Inpatient	0 (0 - 348,976)	0 (0 - 82,004)	0 (-348,976 - 51,775)	0.89
Outpatient	6,367 (4,239 - 15,726)	15,933 (10,957 - 20,906)	6,513 (-69,476 - 43,076)	**<0.0001**

* Wilcoxon Signed Rank Test

Table 5a. Comparing Number of Hospitalizations Pre- and Post-Hydroxyurea by Demographic Variables.

	N	Pre-Hydroxyurea				Post - Hydroxyurea			
Quantiles		25%	50%	75%	95%	25%	50%	75%	95%
Sex									
• Male	42	1	1.5	3	8	0	1	2	5
• Female	49	1	2	3	6	0	1	2	7
Age (years)									
• 0 – 5	32	1	3	4	9	0	1.5	2	5
• 6 – 10	28	1	1.5	3	3	0	1	1	3
• 11 – 15	20	0	1	3	5.5	0	1	1.5	7.5
• >15	11	1	2	5	14	0	0	4	25
Insurance									
• Medicaid	38	0	3	4	14	0	1	2	8
• MM*	9	0	1	3	3	0	1	2	7
• Private	29	1	2	3	4	0	0	2	4
• Mixed	11	0	2	5	11	0	1	2	25

*MM = Managed Medicaid

Table 5b. Comparing Number of Inpatients Days Pre- and Post-Hydroxyurea by Demographic Variables.

	N	Pre - Hydroxyurea				Post - Hydroxyurea			
Quantiles		25%	50%	75%	95%	25%	50%	75%	95%
Sex									
• Male	42	1	5.5	11	30	0	1	8	21
• Female	49	3	6	14	23	0	2	7	26
Age (years)									
• 0 – 5	32	4.5	8.5	13	39	0	3.5	7.5	21
• 6 – 10	28	1	4.5	10	18	0	1.5	5	11
• 11 – 15	20	0	4.5	10.5	30	0	2	8.5	28
• >15	11	1	8	18	83	0	0	21	79
Insurance									
• Medicaid	38	2	6	15	42	0	2.5	7	30
• MM*	9	1	5	8	10	1	6	9	25
• Private	29	3	7	12	18	0	0	7	12
• Mixed	11	0	6	18	83	0	2	8	79

*MM = Managed Medicaid

Table 6: Multivariable Modeling – Effects of Hydroxyurea on Hospitalizations and Inpatient Days by Age.

	Age Group	N	Rate Ratio (Confidence Interval)	P Value
Hospitalizations				
	0-5	32	0.46 (0.30-0.69)	**0.0003**
	6-10	28	0.46 (0.26-0.81)	**0.007**
	11-15	20	0.97 (0.54-1.72)	0.91
	>15	11	1.04 (0.62-1.74)	0.90
Inpatient Days				
	0-5	32	0.44 (0.28-0.69)	**0.0006**
	6-10	28	0.44 (0.24-0.78)	**0.006**
	11-15	20	0.73 (0.41-1.29)	0.28
	>15	11	0.82 (0.49-1.45)	0.43