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Predictors Of Use Of Hydroxyurea And Its Impact On Clinical And Economic Outcomes Among Children With Sickle Cell Disease

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PREDICTORS OF USE OF HYDROXYUREA AND ITS IMPACT ON CLINICAL AND ECONOMIC OUTCOMES AMONG CHILDREN WITH SICKLE CELL DISEASE

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ABSTRACT

Objective: The objective of this study was to assess the prevalence and predictors of use of hydroxyurea (HU) and its impact on clinical and economic outcomes in pediatric patients with sickle cell disease (SCD) enrolled in Medicaid.

Methods: A cohort of patients with SCD was identified in 2006 using ICD-9-CM codes from Medicaid claims from 40 US states. Patients who filled three prescriptions of HU in within 6 months in 2007 were identified as HU users. HU users were then matched with non-users and the impact of HU use on the presence of crises and economic outcomes including presence of hospitalizations and emergency department visits were assessed using conditional logistic regression stratified on matched pairs. Length of stay and medical costs were compared in the matched sample using generalized linear models. An additional clinical outcome, number of crises, was evaluated in the unmatched sample of HU users and non-users using conventional multivariable regression. Estimates obtained using this approach, were then compared with those obtained by minimizing selection bias using regional variation and physician preference-based instrumental variables (IVs).

Results: Prevalence of HU use in children with SCD enrolled in Medicaid was found to be 10.72%. Age, gender, race, disease severity, previous office visits, presence of a comprehensive sickle cell center within the state of residence, and prior opioid use were all found to be significant predictors of HU use in this population ($p<0.0001$). HU users had a significantly greater likelihood of having a hospitalization (OR:2.09; 95% CI:1.28-3.43) and a longer LOS

(β=0.49; 95% CI:0.14-0.84) compared to non-users. Even though the conventional multivariable model showed that HU users had a significantly greater number of crises compared to non-users (β=0.93; p<0.0001), analysis using IVs found no statistically significant relationship (β=-2.75; p=0.2013).

Conclusion: HU use is not very prevalent among children with SCD enrolled in Medicaid. Based on the identified predictors, it seems that physicians follow guidelines when prescribing HU in this population. Since this study failed to corroborate the benefit associated with the use of HU on clinical outcomes and resource utilization, physicians should be wary in prescribing HU in this population.

DEDICATION

This dissertation is dedicated to my home away from home - The Department of Pharmacy Administration at the University of Mississippi

LIST OF ABBREVIATIONS AND SYMBOLS

HU	Hudroxyurea
SCD	Sickle Cell Disease
LOS	Length of Stay
IV	Instrumental Variable
OR	Odds Ratio
CI	Confidence Interval
SD	Standard Deviation
RBC	Red Blood Cell
VOE	Vaso-occlusive Event
ACS	Acute Chest Syndrome
CDC	Centers for Disease Control and Prevention
NIH	National Institutes of Health
ED	Emergency Department
NEDS	Nationwide Emergency Department Sample
CHF	Congestive Heart Failure
MSH	Multicenter Study of Hydroxyurea
NHLBI	National Heart, Lung, and Blood Institute
ResDAC	Research Data Assistance Center

CMS	Centers for Medicare and Medicaid Services
MAX	Medicaid Analytic Extract
ICD-9-CM	International Classification of Diseases, ninth revision, clinical modification
CPT-4	Current procedural terminology 4th edition
HCPCS	Healthcare common procedure coding system
NDC	National Drug Classification
IRB	Institutional review board
DUA	Data Use Agreement
MCO	Managed Care Organization

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CHAPTER 1

INTRODUCTION

This introductory section provides an overview of sickle cell disease (SCD), describes the epidemiology, disease burden, quality of life, and mortality in SCD, explores management options for SCD, and also provides an overview of hydroxyurea (HU), a drug used in patients with SCD. This section concludes with specific aims and significance of this study.

Overview of SCD

SCD is a genetic disorder of the blood characterized by abnormal red blood cells (RBCs). SCD is primarily caused by mutations in the gene for hemoglobin, the iron-containing oxygen-carrier protein in the blood. In normal individuals, RBCs are composed of hemoglobin 'A' due to which they are soft and round. This allows RBCs to easily move through blood vessels. RBCs of patients with SCD develop abnormal hemoglobin proteins (such as 'hemoglobin S', 'hemoglobin C', etc.) which make the RBCs 'sickle'-shaped and cause a decrease in their flexibility while passing through blood vessels.[1] Sickle-shaped RBCs have a tendency to get lodged in blood vessels resulting in decreased blood flow to limbs and other organs. This causes episodes of pain commonly termed as vaso-occlusive events or crises (VOEs), and other complications including episodes of acute chest syndrome (ACS), chronic organ damage, infections, splenic sequestration, anemia, renal and genitourinary issues, and priapism.[1] Individuals of African descent exhibit the highest likelihood of developing the disease.[2] SCD is also common among patients with lineage in South America, the Caribbean, Central America, Saudi Arabia, India, and Mediterranean countries such as Turkey, Greece, and Italy.[3]

Types of SCD

People suffer from several different sub-types of SCD depending on the genotype. Sickle Cell Anemia (HbSS), Sickle-Hemoglobin C Disease (HbSC), Sickle-Beta Thalassemia (HbS beta Thalassemia) are the most common types of SCD.[4]

HbSS: People with this form of SCD inherit two genes for abnormal hemoglobin 'S', one from each parent. In this case, the affected individual has most or all of the normal hemoglobin (HbA) replaced with the sickle hemoglobin (HbS). HbSS is the most common and usually the most severe form of the disease. Severe and chronic anemia is a common characteristic for patients with HbSS along with risk of complications such as VOEs, organ damage, and infections.

HbSC: People who have this form of SCD inherit a gene for abnormal hemoglobin 'S' from one parent and a gene for abnormal hemoglobin 'C' from the other parent. Hemoglobin 'C' results in the development of RBCs called target cells where there is a decrease in the mean hemoglobin concentration. Once the sickle hemoglobin 'S' is combined with the target cell, some mild to moderate anemia may occur. People with this subtype also suffer from some of the complications associated with HbSS, but to a milder degree. VOEs, organ damage, and high risk for infection may also occur in patients with HbSC.

HbS beta-Thalassemia: People with this form of SCD inherit a gene for abnormal hemoglobin 'S' from one parent and a gene for beta-thalassemia from the other parent. There are two types of beta thalassemia: '0' and '+'. People with HbS beta 0-thalassemia usually have a severe form of SCD while those with HbS beta +-thalassemia tend to have

a milder form of SCD. This subtype of SCD produces symptoms of moderate anemia and many of the same complications associated with HbSS, but to a milder degree.

HbSD, HbSE, and HbSO: These are comparatively rarer forms of SCD. People who have these forms of SCD inherit one gene for abnormal hemoglobin 'S' and one gene for an abnormal type of hemoglobin including 'D', 'E', or 'O'. Often, the signs and complications of these subtypes are similar to those of a person with the HbSS subtype.

Sickle cell trait: In addition to the subtypes described above, patients might suffer from sickle cell trait. Patients with sickle cell trait are carriers of the disease, but do not have SCD. Individuals with sickle cell trait carry the gene for defective hemoglobin (HbS) but also have some normal hemoglobin (HbA). Mild anemia may occur although patients with sickle cell trait are usually without symptoms of the disease. Under intense stressful conditions, exhaustion, hypoxia (low oxygen), and/or severe infection may occur.

Clinical manifestations of SCD

Patients with SCD often suffer from life-threatening complications including VOEs (acute episodes of pain), episodes of ACS, stroke/cerebral infarction or hemorrhage, infections, splenic sequestration, anemia, renal and genitourinary issues, avascular necrosis, cholelithiasis, and ophthalmologic complications. A study by Loureiro et al. using records of adolescents and adults with SCD from a public teaching hospital in Brazil found that acute episodes of pain were the most common complication of SCD (71.7% in adolescents and 75% in adults), followed by ACS (10.4% in adolescents and 6.5% in adults).[5] Stroke is one of the highest known causes of death in SCD patients.[6] VOEs, ACS, and strokes are the most common complications in the

pediatric population. SCD in combination with these complications may impose a significant burden on the patient, payers, and the society.

The burden of the above mentioned clinical manifestations of the disease will not be realized until the epidemiology of SCD is known. The next section provides a detailed description of the epidemiology of SCD.

Epidemiology of SCD

SCD is the most common hereditary disorder of the blood in the United States. The Registry and Surveillance System for Hemoglobinopathies (RuSH) project is a collaborated effort between the Centers for Disease Control and Prevention (CDC), The National Institutes of Health (NIH), and seven states including California, Florida, Georgia, North Carolina, New York, Michigan, and Pennsylvania to understand the epidemiology and burden of SCD. According to their report, SCD affects a total of 90,000 to 100,000 Americans.[3] The incidence of SCD is 1 out of every 375 to 600 African-American and 1 out of every 2,000 Hispanic-American births.[7] Overall, the life expectancy for SCD patients is 42 years in men and 48 years in women.[6] A study conducted using the US Census population data reported that in 2005 there were 89,079 people with SCD in the US of which 80,151 were African Americans and 8,928 were Hispanics.[8] Another study involving analysis of the Florida Medicaid claims found that 70% of all identified SCD patients were African-American.[9] The state with the highest population of SCD patients was New York with 8,308 people, followed by Florida with 7,539 people, and Texas with 6,765 people. A more recent study conducted using the 2008 US census data reported that national SCD population estimates ranged from 72,000 to 98,000 when adjusted for SCD mortality in adults.[10] Some variation in the prevalence of SCD was also seen

in terms of the phenotypes. In African-Americans, the birth prevalence of sickle cell anemia (HbSS) is 1/375, of HbSC is 1/835, and of HbS/beta thalassemia is 1/1667.[11]

The next section reviews the literature pertaining to the burden associated with SCD. Specifically, the economic burden and healthcare resource utilization associated with the disease will be described.

Burden associated with SCD

Studies associated with disease burden of SCD provide information regarding two parameters, namely, the economic burden and healthcare resource utilization associated with the disease.

Economic burden of SCD

SCD imposes a significant economic burden on patients, payers, and the society.[12] It is estimated that annual charges for an adult with sickle cell disease are $231,050 while children with SCD may incur $203,813 per patient per year.[13] Woods et al. analyzed a statewide administrative dataset in Illinois (1992-1993) which consisted of 8,403 hospital admissions for 1,189 SCD patients.[14] Total hospitalization charges for these patients were found to be more than $30 million per year. Kauf et al. analyzed Florida Medicaid data from 2001-2005 and found that the average total cost per patient-month for SCD was $1,946.[9] For an average SCD patient surviving till the age of 45, total undiscounted health care costs were estimated to be $953,640.

Previous studies have attempted to assess costs/charges for inpatient care pertaining to SCD in adults. Davis et al. analyzed data from the National Hospital

Discharge Survey from 1989 to 1993.[15] The average cost per SCD-related hospitalization (in 1996 dollars) was estimated to be $6,300, resulting in an annual direct cost of approximately $475 million per year. Similar costs were reported by Mayer et al. who reported results from hospital data from the 1994 American Hospital Association (AHA) survey.[16] Nietert et al. analyzed data from the Sickle Cell Program at the Medical University of South Carolina (MUSC) and the MUSC-affiliated Charleston Memorial Hospital from January 1, 1996 to September 20, 1997.[17] The authors found that the mean inpatient and physician charges for an SCD-related admission were $7,290 and $1,589, respectively. In addition, it was found that a small proportion of patients (4.2%) were responsible for a large portion (40%) of the aggregate total charges. This indicates that patients with severe disease incur significantly higher costs as compared to those with less severe disease.

Emergency department (ED) visits are a significant contributor to costs in adult patients with SCD. Lanzkron et al. analyzed the Nationwide Emergency Department Sample (NEDS) for calendar year 2006.[18] Costs for patients with SCD were compared to those with other chronic conditions such as asthma, congestive heart failure (CHF), and HIV. For hospitalizations associated with an ED visit, the charges per 100 SCD patients (1.5 million) were higher than those incurred by patients with CHF ($500,000), HIV ($281,818) and asthma ($14,411). However, the mean charges per ED visit for patients with SCD were on the lower side ($21,679) while patients with CHF, asthma, and HIV incurred $29,317, $16,485, and $50,753 respectively. Hence, it is essential to note that the reason for high economic burden due to ED visits in SCD patients as compared to other conditions is the high frequency of ED visits rather than the expensive care.

The studies described so far report the economic burden of SCD in the adult population. There are relatively fewer studies which assess the economic burden of SCD in children. Although pediatric SCD patients incur lower costs as compared to adults, the burden is still substantial.[9]

Mvundura et al. assessed expenditure for US children with SCD using the Marketscan® Medicaid Database and the Marketscan® Commercial Claims and Encounters Database for calendar year 2005.[19] Interestingly, even though the percentage of SCD children enrolled in Medicaid with an inpatient admission was higher as compared to patients with private insurance (43% vs. 38%), mean expenditure per admission was lower for children enrolled in Medicaid ($6,469 for Medicaid vs. $10,013 for private insurance). This may be an indication of lower reimbursements by Medicaid. The total annual expenditure for pediatric Medicaid patients was reported to be $11,075, while that for privately insured patients was $14,722.

Bilenker et al. compared expenditures for children with and without SCD in the Washington State Medicaid program.[20] In 1993, children with SCD had mean expenditures 8.8 times that of the non-SCD children. Also, 10% of children with the highest expenditures accounted for 56% of the expenditures. Out of the total expenditures, 72% were attributed to inpatient care, followed by outpatient care (11%), physician payments (11%), and only 3% for prescription drugs.

In an attempt to assess the national economic burden of children with SCD, Amendah et al. analyzed the 2005 MarketScan® Medicaid and Commercial Claims database.[21] It was found that Medicaid children with SCD incurred medical expenses that

were $9,369 higher than children without SCD. A similar trend was seen for privately insured beneficiaries with SCD children costing $13,469 higher than those without SCD.

Healthcare resource utilization in SCD

The primary source of hospital admissions for adult patients with SCD is emergency rooms.[14] A study conducted using the Illinois Hospital Association administrative claims data reported that SCD patients had ED as the primary source of admission in 85.7% of the claims.[14] The median number of ED admissions per SCD patient was three, which may not be considered high since this was reported over a period of two years. Aisiku et al. compared SCD patients who were high ED utilizers (defined as at least 3 ED visits per year) with low utilizers.[22] Only 35.5% patients with SCD were found to be high utilizers of the ED. However, these patients were more severely ill (as measured by laboratory variables), had more pain and distress, and had a lower quality of life than SCD patients who were low utilizers of ED visits. Lanzkron et al. reported the incremental burden associated with SCD as compared to other chronic conditions.[18] Patients with SCD were found to have the most number of ED admissions per 100 patients (68.4) as compared to patients with asthma (1.1), HIV (5.1), and CHF (17.3). Epstein et al. analyzed data from the SCD program at Thomas Jefferson University Hospital.[23] The 20% highest inpatient service utilizers accounted for 54% of ED visits resulting into a hospitalization, 52% of ED visits only, 54% of hospital bed days, and 24% of office visits. The ED was a common source of health service utilization, with a mean of 7.4 visits per patient year, a third of which resulted in a hospital admission. The frequency of ED visits reported in this study is higher than that reported by Woods et al.[14] This is probably due to the fact that this study included patients who were receiving SCD

care for more than three years at Thomas Jefferson University Hospital. Since this study may be analyzing data from severely ill patients, the frequency of ED visits per patient per month might have been higher compared to other studies.

Hospital admissions are also a common mode of healthcare resource utilization among patients with SCD. A study by Davis et al. reported that in the US, the total number of hospitalizations for SCD patients was 75,000 per year.[15] Brousseau et al. analyzed the 2005 and 2006 Healthcare Cost and Utilization Project (HCUP) State Inpatient Databases and State Emergency Department Databases.[24] The 21,112 patients with SCD had an average of 1.52 encounters for hospitalizations and 1.08 for treat-and-release ED visits per patient per year. As expected, average health service utilization was highest for patients with public insurance (3.22 encounters per patient per year) as compared to privately insured (1.76 encounters per patient per year) and uninsured patients (1.42 encounters per patient per year).

Relatively fewer studies have examined SCD-related healthcare resource utilization in children. A study using the Nationwide Emergency Department Sample (NEDS) reported a total of 44,188 pediatric visits in 2006 due to SCD.[18] Glassberg et al. analyzed data from the Silent Cerebral Infarct Transfusion (SIT) trial which identified children with SCD in the United States, Canada, England, and France.[25] Only 0.74 ED visits per pediatric patient per year were identified in this study. Risk factors for increased ED visits included a history of asthma and ACS. A study by Panepinto et al. conducted using the 1997 HCUP Kid's Inpatient Database (KID) reported a total of total of 20,271 hospital discharges and length of stay (LOS) of 4.4 days in SCD children with VOEs in the US.[26] Older age was associated with higher frequency of hospitalizations

and longer hospital stays. Leschke et al. analyzed Wisconsin Medicaid claims (2003-2007) and reported that the 14-day and 30-day re-hospitalization rates in children with SCD were 10.21% and 17.2% respectively.[27]

The next section provides an overview of studies addressing the impact of SCD on patient quality of life and mortality.

Quality of life and mortality in SCD

In addition to its clinical and economic impact on patients, SCD has a significant effect on patients' quality of life due to its long-lasting clinical manifestations. An exploratory study in London found that SCD carries a huge psychosocial burden impacting physical, psychological, social and occupational well-being in patients with SCD.[28] In another study, McClish et al. administered the Short Form 36 (SF-36) scale to 308 patients with SCD to determine the health related quality of life (HRQOL) in this population.[29] SCD patients scored significantly lower than national norms on subscales including physical function, physical and emotional role function, bodily pain, vitality, social function, and general health. When compared to asthma, SCD patients had similar scores on physical function, role function, and mental health domains, but lower scores for bodily pain, vitality, social function, and general health subscales.

Panepinto et al. presented child and caregiver reports of HRQOL in pediatric patients with SCD.[30] Compared with child reports, caregivers reported significantly worse HRQOL in SCD patients in the overall perception of health, physical functioning, behavior, and self-esteem domains ($p < 0.005$). High correlation in parent and child reports was found in bodily pain ($r = 0.58$), while domains including physical functioning ($r = 0.44$), behavior ($r = 0.45$), general health ($r = 0.44$), self-esteem ($r = 0.40$) and changes in health ($r = 0.33$) were moderately

correlated. Also, factors including disease status, neurobehavioral co-morbidities, and parent education were found to be predictors of HRQOL in children with SCD. Palermo et al. compared caregiver-reported HRQOL for children with SCD with caregiver-reported HRQOL of healthy children.[31] Caregivers of children with SCD reported that their children had lower physical, psychological, and social well-being than children without SCD.

SCD is also associated with a significant burden of mortality. A study conducted using 1995-2005 Tennessee Medicaid claims indicated that mortality rates in SCD patients are significantly higher as compared to non-SCD African-American beneficiaries.[32] A cohort study using data from 1987 to 1996 reported that the median survival was 53 years for men and 58.5 years for women with SCD.[33] The burden of mortality differs by patient demographic characteristics. In the US, the highest rate of SCD-related mortality has been reported in Washington D.C.[2] Seizures, acute anemic episode, renal failure, VOEs, and ACS are some predictors of mortality identified in the literature.[6,34]

Management of SCD has been the focus of all healthcare strategies given its substantial burden on the diseased population. The next section describes an overview of management strategies for SCD. Specifically, the role of sickle cell centers and treatment options in the management of SCD will be described.

Management of SCD

Treatment options

Timely and effective treatment is an important factor in reducing morbidity and mortality associated with SCD. However, limited treatment options are available for patients with SCD.

Blood transfusion and stem-cell transplants are among the most expensive options used mainly as secondary therapies to treat patients with advanced disease.[35] Transfusions result in an increase in the oxygen carrying capacity of the blood and maximize the number of normal RBCs in circulation which helps in correcting anemia.[36] Patients on blood transfusion programs have been found to have a reduced incidence of stroke.[37] Stem cell or bone marrow transplantation remains the definitive treatment for complete cure and eradication of the disease. In patients with SCD, transplantation of healthy bone marrow from a genetically-matched donor can lead to the production of normal hemoglobin and an eventual reversal of the disease.[38]

In the late 1980s and early 1990s, researchers began investigating the potential of hydroxyurea (HU), an anti-neoplastic agent, in reducing the frequency and severity of crises in SCD.[39,40] HU was initially approved for treating chronic myeloid leukemia, polycythemia vera, and essential thrombocythemia. The efficacy of HU to reduce symptoms of SCD was established in 'The Multicenter Study of Hydroxyurea in Sickle Cell Anemia' trial (MSH trial) in 1995 which reported that HU reduced the annual rate of painful events, episodes of ACS, and blood transfusions in patients with SCD.[41] As a

result, this drug was approved by the FDA in 1998 for the treatment of SCD in adults. Although HU has not been approved for use in pediatric patients, it is recommended in this population due to its proven safety and efficacy in reducing clinical events in children with SCD.[42–44] In a longitudinal study by Ferster et al. (2001) using the Belgian SCD registry, HU use was associated with a significant reduction in hospitalizations in children with SCD.[45] Studies have also documented that therapy with HU results in a decrease in the number of blood transfusions per patient.[46,47]

According to the guidelines published by the National Heart, Lung, and Blood Institute (NHLBI), HU is indicated for children (after consultation with parents and expert pediatricians) with SCD experiencing frequent pain episodes, history of acute chest syndrome, or severe symptomatic anemia.[48] Specifically, HU is indicated for use in children who are three years of age or older; have more than two severe VOEs per year; have more than two episodes of ACS per year; or any combination of greater than two episodes of ACS per year and severe pain.[49] The guidelines also state that no improvement is expected until the drug has been taken daily for 3-6 months. It is recommended that HU be initiated and monitored by hematologists since long-term HU use may result in long-term toxicity.

Sickle cell centers

People affected by SCD require comprehensive care which involves holistic, multi-disciplinary management of their disease. The components of comprehensive care for patients with SCD include patient/parent/caregiver information, genetic counseling, social services, prevention of infections, dietary advice and supplementation,

psychotherapy, renal and other specialist care, pain control, physiotherapy, drug dependency services and specialist sickle cell nursing.[50,51] The NIH supports 10 comprehensive sickle cell centers in the United States which carry out SCD-related research and patient-centric activities focusing on the implementation of best models to treat and care for patients with SCD. In addition, there are several specialized sickle cell clinics across the US which provide care to patients with SCD. Since the goal of these comprehensive care centers and clinics is to increase access to SCD care, they play a vital role in improving outcomes among patients with the disease.

HU therapy in SCD

Mechanism of action of HU

Although the exact mechanism of HU in treating patients with SCD is unknown, it is believed that HU increases the production of hemoglobin F (HbF) in RBCs.[52] HbF is the main hemoglobin in the fetus during the last seven months of uterine development and in the newborn until roughly six months after birth. HbF prevents the polymerization of sickle cell hemoglobin which inhibits their sickling. By increasing the production of HbF in RBCs, it prevents the malformation of RBCs which increases the overall proportion of normally structured RBCs in circulation thus reducing complications associated with the disease.[40] Low HbF is one of the predictors of early mortality in patients with SCD.[44] As a result, HU use not only has the potential to reduce clinical events in SCD patients, but also to increase life expectancy.

Utilization of HU and its impact on outcomes

Despite the MSH and other studies providing evidence for the efficacy of HU, it is underutilized in the adult as well as the pediatric population, thus limiting its effectiveness.[53] An observational study conducted in the Florida Medicaid claims data reported that only 38% of adult SCD patients eligible to receive HU had a prescription claim for the same.[54] The utilization of HU is even lower (approximately 8%) in children as demonstrated by a study conducted in the South Carolina Medicaid population.[55] Current research does not provide an estimate of HU use in a nationwide sample of SCD patients. Also, it is necessary to assess predictors of HU use in the population using real-world data in order to be able to increase the utilization of HU.

The MSH was the biggest trial to date which provided evidence of the efficacy of HU treatment in adults with SCD.[41] It was reported that the median time to the first crisis (3.0 vs. 1.5 months; $p=0.01$) and the second crisis (8.8 vs. 4.6 months; $p<0.001$) was longer in the HU treatment group as compared to the non-treatment group. It was also reported that fewer patients assigned to hydroxyurea had chest syndrome (25 vs. 51, $p<0.001$), and fewer underwent transfusions (48 vs. 73, $p=0.001$). While the impact of HU on clinical events is substantial, other studies also show that use of HU decreases healthcare resource utilization and costs in the adult SCD population.[56]

While there is some evidence to suggest that HU use is associated with improvement in SCD-related clinical outcomes among children, studies documenting such effects are mainly clinical trials recruiting a highly restricted sample.[39,42,57] There is a scarcity of real world research demonstrating the effect of HU use in the pediatric SCD

population. Only one observational study has attempted to assess the association between HU use and clinical outcomes in children using the South Carolina Medicaid administrative claims data.[58] HU users were found to have significantly more vaso-occlusive crises than non-users. These results are not in accordance with the results obtained in pediatric clinical trials demonstrating the effect of HU use on clinical complications in SCD. Research is also lacking in terms of investigating the impact of HU use on economic outcomes including healthcare resource utilization and costs in the pediatric population. It is important to fill these gaps in research and provide real-world evidence regarding the relationship between HU use and clinical and economic outcomes in children with SCD.

The purpose of this study was to assess the prevalence of HU use in the pediatric population with SCD and to examine the predictors of HU use in this population. In addition, this study assessed the relationship between HU use and clinical and economic outcomes in children with SCD. The author used the 2006-2008 Medicaid administrative claims data for 40 US states (all US states except Hawaii, Montana, Pennsylvania, Utah, Wisconsin, Washington DC, Wyoming, Alaska, Missouri, North Dakota, and South Dakota) for the purpose of this study.

SCD is mainly prevalent in the African-American and Hispanic population, which represent almost 50% of beneficiaries enrolled in Medicaid programs nationwide.[59] Also, pediatric beneficiaries contribute to a high 58% of the national Medicaid population.[60] Previous research has documented that the majority of SCD patients seeking healthcare are covered by government insurance.[14,15] Given the lower than average life-span of

those suffering from the disease, it is reasonable to assume that most of these patients are in fact covered by Medicaid. As a result, Medicaid claims data were the appropriate choice for obtaining a representative sample of pediatric SCD patients.

Specific aims

The specific aims of this study were:

1. To examine HU use among a cohort of children with SCD in the Medicaid population.
    a. To determine the prevalence of HU use.
    b. To assess demographic and health-related predictors of HU use including age, gender, race, SCD severity, prior blood transfusions, prior office visits, prior opioid use, and presence of a comprehensive sickle cell center in the state of residence.
2. To investigate the association between HU use and clinical outcomes among children with SCD in the Medicaid population.
3. To assess the relationship between HU use and healthcare resource utilization in children with SCD in the Medicaid population.
    a. To evaluate the impact of HU use on SCD-specific hospital admissions.
    b. To assess the impact of HU use on length of hospital stay of SCD-specific hospital admissions.
    c. To study the impact of HU use on SCD-specific ED visits.
4. To evaluate the relationship between HU use and SCD-specific direct medical costs in children enrolled in Medicaid.

Significance of this study:

Current literature reporting prevalence of HU use in children with SCD using objective real-world data is very scanty. Objective data provide real-world estimates of medication use rather than self-reported measures which may potentially produce inflated estimates.[61] Only one study by Tripathi et al. has reported estimates for use of HU in the pediatric population using data from South Carolina Medicaid claims.[55] Although this study provided important information regarding the prevalence of HU use among Medicaid beneficiaries in South Carolina, the findings of this study cannot be generalized to the entire Medicaid population.

HU is the only inexpensive treatment option for patients with SCD. Despite this, more than 60% patients who are eligible for HU based on their disease severity do not receive treatment. In their statement on the use of HU in SCD, the NIH panel emphasized the need for effectiveness studies identifying SCD patients that are eligible to receive HU and those who will benefit from it.[62] So far, no study has examined demographic and health-related predictors of HU use in children with SCD. Significant predictors to HU therapy identified from this study can help policy makers target non-users of HU so as to promote effective HU use in this population. Also, this study may help track potential over-use of HU use in this population. Increasing the appropriate use of HU may prove beneficial to both, the SCD patient and the healthcare system. The goal of chapter 2 is to assess the prevalence of HU use among pediatric Medicaid beneficiaries with SCD. In addition, demographic and health-related predictors of HU use will be examined in this population.

Clinical complications associated with SCD, mainly vaso-occlusive crises (sickle cell crises) bear a significant economic and psychological burden on patients and caregivers.[12] The

association between HU use and clinical outcomes has not been explored to a great extent in the pediatric population. Current evidence examining this relationship consists of studies which are small clinical trials with limited generalizability.[45] However, for a treatment to be considered effective, determining its impact on clinical outcomes in a non-controlled real-world setting is extremely crucial. Our study attempts to fill this gap by assessing the impact of HU use on clinical outcomes in pediatric SCD patients enrolled in Medicaid programs nationwide in Chapter 3.

In addition to studying the impact of treatment on clinical manifestations of the disease, it is important to determine whether the treatment of SCD with HU is economical and results in a decrease in healthcare resource utilization. This is particularly useful for health plans in making formulary decisions. A previous study found that HU use was associated with decreased costs, hospitalizations, and ED visits in the pediatric population.[63] Although this study made a significant contribution towards bridging a gap in research, it was conducted in the North Carolina Medicaid population. The state of North Carolina offers specific resources related to SCD that other states may not provide. Specifically, one of the ten NIH-endorsed comprehensive sickle cell centers in the US is located in North Carolina. This may affect HU use as well as clinical and economic outcomes among Medicaid beneficiaries with access to care in these centers. As a result, the findings of this study cannot be generalized to the entire Medicaid population. Chapter 4 assesses the relationship between HU use and healthcare resource utilization and medical costs in the pediatric SCD population enrolled in Medicaid.

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CHAPTER 2

PAPER I

PREVALENCE AND PREDICTORS OF HYDROXYUREA USE AMONG CHILDREN WITH SICKLE CELL DISEASE ENROLLED IN MEDICAID

ABSTRACT

Objective: Hydroxyurea (HU) is approved for use in adult patients with sickle cell disease (SCD) to increase the percentage of fetal hemoglobin in circulation, thus decreasing clinical complications associated with the disease. The goal of this study was to determine the prevalence of HU use and assess the predictors of its use in the pediatric population with SCD enrolled in Medicaid.

Methods: The 2006-2007 Medicaid claims data from 40 US states was extracted. The inclusion criteria for the study sample were enrollment in the Medicaid program for 18 months in calendar years 2006-2007, age less than 18 years, and non-dual eligibility. Patients having two or more medical claims for SCD in 2006 were identified as SCD patients. HU use among these patients was identified using NDC codes from the prescription claims file and was defined as three or more prescriptions of HU in a 6-month period in calendar year 2007. Prevalence of HU use was calculated as number of HU users by the total number of patients with SCD in 2007. Age, gender, race, SCD severity, prior blood transfusions, prior opioid prescriptions, prior office visits, and presence of a comprehensive sickle cell center in the state of residence were tested as predictors of HU use in SAS 9.4 using logistic regression analysis.

Results: A total of 12,213 Medicaid beneficiaries in calendar year 2006 met our inclusion criteria. Of these, 1,309 SCD patients (10.72%) were identified as HU users in 2007. Age (OR:1.12; 95% CI:1.11-1.14), black race (OR:0.73; 95% CI:0.65-0.83), male gender (OR:1.22; 95% CI:1.08-1.37), disease severity (OR:2.16; 95% CI:1.90-2.45), presence of a comprehensive

sickle cell center in the state of residence (OR:1.61; 95% CI:1.42-1.82), prior office visits (OR:1.01; 95% CI:1.01-1.02), and having a prior opioid prescription (OR:2.07; 95% CI:1.80-2.39) emerged as significant predictors of HU use in this study.

Conclusion: Use of HU among children with SCD enrolled in Medicaid is very low, which suggests that physicians exercise caution when prescribing this drug which is not approved for use in this population. Health-related predictors that were indicators of severe disease (disease severity, prior office visits, and prior opioid prescriptions) were found to positively affect HU use which indicates that on average, physicians follow guidelines recommending that HU should only be prescribed in children with severe form of the disease.

INTRODUCTION

Sickle cell disease (SCD) is a blood disorder characterized by the presence of sickle-shaped red blood cells which carry less oxygen to body tissues and can easily get lodged in small blood vessels, thereby leading to clinical complications including stroke, acute chest syndrome (ACS), and painful vaso-occlusive events (VOEs).[1] Hydroxyurea (HU) was first approved for adults with SCD based on clinical trials showing that HU significantly reduces VOEs, episodes of ACS, and frequency of blood transfusions among adult patients with SCD.[2–5] The efficacy of HU in the adult as well as pediatric SCD population was later confirmed by several other randomized trials.[3,6,7] According to the guidelines published by the National Heart, Lung, and Blood Institute (NHLBI), HU is indicated for adults and children (after consultation with parents and expert pediatricians) with SCD experiencing frequent pain episodes, history of acute chest syndrome, or severe symptomatic anemia.[8]

A 2008 Consensus Development Conference Statement by the National Institutes of Health (NIH) identified patient-, caregiver-, provider-, and system- level barriers to HU therapy stating that HU is underutilized among patients with SCD.[9] Several studies have assessed the utilization of HU in the adult SCD population. Lanzkron et al. used the NHLBI guidelines to identify SCD patients eligible for HU therapy in the Maryland Health Services Cost Review Commission database.[10] The authors reported that 70% of the patients with SCD who were eligible for HU therapy were not prescribed the medication. In their analyses of Florida Medicaid claims data, Ritho et al. reported that only 38% of SCD adults who were eligible

received one or more prescriptions of HU during a 5-year period (2001 to 2005).[11] Another study using data from a Maryland Medicaid managed care organization reported that only 14% adults with SCD filled a prescription of HU from 2001 to 2005.[12] Of these, 44% of the patients filled 1–3 HU prescriptions and 29% filled 4–12 HU prescriptions, while only 27% of the patients filled 13 or more prescriptions of HU.

Studies reporting HU use in children with SCD are relatively few in number. A self-administered survey conducted among caregivers of children with SCD recruited from five pediatric hematology centers in the north-east USA found that only 38% of children with SCD were receiving HU therapy.[13] An apparent limitation of this study is the use of self-report measures for HU use which may have resulted in biased estimates.[14] Tripathi et al. used 1996-2006 South Carolina Medicaid administrative claims to obtain an objective measure of HU use in children. It was found that of the 2,194 children with SCD enrolled in South Carolina Medicaid, only 175 (8.0%) received HU treatment.[15] The mean duration of HU therapy was 870 days (standard deviation [SD] = 770 days), the median being 669 days.

A few studies have assessed the prescribing patterns among providers of SCD patients (adults as well as children). Zumberg et al. assessed the prescribing patterns of HU for SCD by surveying hematologists in Florida and North Carolina.[16] It was found that approximately 55% of the hematologists prescribed HU in 10% of their SCD patients. Brandow et al. evaluated prescribing patterns for HU by surveying members of the American Society of Pediatric Hematology/Oncology.[17] Of the providers that cared for SCD patients, only 9% reported that 50-90% of their SCD patients had received HU, while 10% physicians reported that less than 10% patients had received HU. The criteria used for prescribing HU were a diagnosis of ACS and greater than two episodes of pain per year. In summary, although clinical trials have

demonstrated that HU is effective in decreasing pain and other symptoms of SCD, its utilization among pediatric SCD patients is low.

Research suggests that several demographic factors could affect HU use in the SCD population. Lanzkron et al. found that that males with SCD were significantly more likely to use HU as compared to females (22% vs. 12%, p=0.01).[12] Also, HU use was found to be significantly higher among younger as compared to older adults (mean age: 28 years vs. 32 years, p=0.02).[12] It is well established in the literature that minorities receive a lower quality of care than the White population in the US health care system, even after controlling for social determinants and insurance status.[18,19] Although not demonstrated in the SCD population, race/ethnicity may be a potential predictor of HU use in this population.

In addition to demographic factors, health-related factors may affect HU use in patients with SCD. According to the guidelines for HU use in the pediatric population, HU is indicated in pediatric SCD patients (1) having more than two severe VOEs per year, OR (2) having more than two episodes of ACS per year, OR any combination of (1) and (2) amounting to greater than two episodes per year.[20] In the previously mentioned study by Zumberg et al., it was found that the most common reasons cited for prescribing HU in the SCD population were frequent painful crises (76%), chronic pain with frequent narcotic use (58%), and acute chest syndrome (43%).[16] This is an indication that SCD severity may be a determinant of HU use; patients with severe disease are more likely to be prescribed HU. Blood transfusions are an alternative course of treatment in patients with SCD which are both, time consuming and expensive. In a cross-sectional study conducted among adults with SCD enrolled in Florida Medicaid, Ritho et al. found that prior blood transfusions were a significant predictor of HU given that 73% patients in the HU cohort had a prior blood transfusion as compared to 59% in the non-HU cohort (χ^2 =

16.3; $p < 0.0001$).[11] Since this study was conducted in the adult population with SCD, it cannot be said with certainty that this relationship will hold true in the pediatric population. In a survey of parents of children suffering from SCD, Oyeku et al. reported that current HU users had significantly greater prior physician office visits as compared to non-HU users ($p<0.001$).[13] Contradicting this result, Candrilli et al. reported that prior physician office visits were significantly greater in patients who were non- adherent to HU.[21] Although prior office visits represent greater access to care (which may be associated with increased medication use), they can also be an indicator of poor health which may be associated with lower HU use. Patients with SCD generally use opioid analgesics to curb the pain from episodes of vaso-occlusive crises. In the previously mentioned survey by Zumberg et al. conducted in community-based practices, frequent pain with narcotic use was one of the top reasons for physicians to prescribe HU. Patients with prior opioid use can be expected to have a greater likelihood of HU use, as these patients may be suffering from a more severe form of the disease. At the same time, opioids may help in reducing pain from sickle cell crises, which may result in lower HU use among patients using opioid analgesics. The directionality of the relationship between prior opioid use and using HU among SCD patients remains to be examined. A well-known barrier to HU use in children with SCD is non-compliance, which may be a result of poor access to care.[17] The NIH supports 10 comprehensive sickle cell centers located across eight states in the United States. Two centers are located in Pennsylvania and California, while Ohio, Texas, New York, North Carolina, Massachusetts, and Tennessee have one center each. Since the purpose of these centers is to carry out patient-centric activities focusing on the implementation of best models to treat and care for patients with SCD, it can be expected that the use of HU is more prevalent among patients living in these states. Although comprehensive sickle cell centers are known to

improve outcomes, their impact on medication use among children with SCD has never been assessed.[22,23]

No previous study has attempted to assess the prevalence and predictors of HU in pediatric SCD patients nationally enrolled in Medicaid. Medicaid beneficiaries are known to have poorer overall health, lower income, and lower access to prescription drugs compared to the US population.[24] As a result, studies conducted in other patient populations cannot be generalized to Medicaid beneficiaries. Also, studies conducted in the adult population cannot be extended to the pediatric population with SCD due to differences in treatment guidelines and disease management strategies. The objectives of this study were to assess the prevalence of HU and to identify predictors of HU use among children with SCD enrolled in Medicaid programs nationwide.

METHODOLOGY

Data source

Medicaid is a state-operated, federally-funded program providing healthcare coverage for low-income individuals and families. Medicaid administrative claims data are made available for research purposes through the Research Data Assistance Center (ResDAC), a contractor for Centers for Medicare and Medicaid Services (CMS) that provides de-identified data in the form of Medicaid Analytic Extract (MAX) files.

The 2006-2007 Medicaid analytic extract (MAX) files for 40 US states (all US states except Hawaii, Montana, Pennsylvania, Utah, Wisconsin, Washington DC, Wyoming, Alaska, Missouri, North Dakota, and South Dakota) were used for the purpose of this study. Information regarding Medicaid enrollment, utilization, and expenditures is made available through the MAX personal summary, inpatient claims, other services, and pharmacy claims files. The MAX personal summary file contains person-level demographic and eligibility data for Medicaid beneficiaries. The MAX inpatient claims file is an event level file with information regarding the admission and discharge dates, payment amount, International Classification of Diseases, ninth revision, clinical modification (ICD-9-CM) diagnoses codes (up to ten fields), and ICD-9-CM current procedural terminology 4th edition (CPT-4) or healthcare common procedure coding system (HCPCS) procedure codes (up to seven fields). The MAX other services file is an outpatient facility visit-level file with information regarding physician services, clinic services, ICD-9-CM diagnoses codes (up to two fields), and CPT-4 and HCPCS procedure codes (one

field), provider identification number, date of service, place of service, and payment amount. Information from outpatient (non-institutional) facilities including outpatient hospital, physicians' office, and emergency department is included in this file. The MAX pharmacy claims file is a prescription-level file with information regarding National Drug Classification (NDC) codes, days of supply for prescribed medication, quantity of drug dispensed, prescription date, prescribing physician ID and payment amount. All the files mentioned above can be linked by a common encrypted beneficiary ID. Approval to conduct this project was sought from the institutional review board (IRB) at the University of Mississippi. After this, a data use agreement (DUA) was made with CMS through ResDAC.

Patient selection

The sample for this study consisted of Medicaid enrollees from 40 US states (all US states except Hawaii, Montana, Pennsylvania, Utah, Wisconsin, Washington DC, Wyoming, Alaska, Missouri, North Dakota, and South Dakota) who were enrolled in the Medicaid program for 18 months in calendar years 2006-2007 and who were less than 18 years of age. Dual-eligible beneficiaries who were enrolled simultaneously in Medicaid and Medicare were excluded from this study. The reason for their exclusion is that beneficiaries with coverage under both the plans may have incomplete claims in the data, and certain events may not have been reflected in their Medicaid claims records. Although physical impairment in patients with SCD may begin at childhood, it is unlikely that children will qualify for Medicare due to disability at such a young age.[25] As a result, it is not anticipated that excluding dual-eligible beneficiaries will significantly bias the results. Since HU was initially approved to treat chronic myeloid leukemia (ICD-9-CM code 205.1), polycythemia vera (ICD-9-CM code 238.4), and

essential thrombocythemia (ICD-9-CM code 238.71), patients with a diagnosis code for these conditions were excluded from the study.

Calendar year 2006 served as a cohort identification period for this study. Patients having two or more medical claims for SCD in 2006 indicated by ICD-9-CM codes in Appendix A, Table 1 were identified as SCD patients. Among these patients, HU use was identified using NDC codes presented in Appendix A, Table 2 from the prescription claims file.

Measures

HU use was defined as three or more prescriptions of HU in a 6-month period in calendar year 2007. The reason for this was that the guidelines for HU use in children state that no improvement is expected until the drug has been taken daily for 3-6 months. A measure of HU use any less frequent than this may result in inclusion of patients with extreme under-utilization of HU and may bias the results.

Prevalence of HU use among pediatric Medicaid beneficiaries with SCD was calculated in calendar year 2007 as follows:

$$\text{Prevalence of HU use} = \frac{\text{Number of HU users}}{\text{Total number of patients with SCD}} \times 100$$

Potential predictors of HU use including age, gender, race, SCD severity, prior blood transfusions, prior opioid prescriptions, prior office visits, and presence of a comprehensive sickle cell center in the state of residence were evaluated. Age was calculated as age at the end of calendar year 2007 and was used as a continuous variable in the analysis. Gender was

measured as a categorical variable with categories male and female. Race was used as categorical variable. It was categorized as Black and non-Black (consisting of White, Hispanic or Latino, Asian, Native Hawaiian or other Pacific Islander, American Indian or Alaskan Native, or unknown race). SCD severity was measured as a binary variable in calendar year 2006. Patients with (1) three or more severe vaso-occlusive pain events, OR (2) three or more episodes of acute chest syndrome, OR any combination of (1) and (2) amounting to three or more episodes were classified as having severe SCD. All others were classified as having less severe disease. Prior blood transfusions were coded as a binary categorical variable depicting the presence or absence of a claim for a blood transfusion in the inpatient claims and other services files. Blood transfusions were identified using CPT-4, HCPCS procedure, and revenue codes provided in Appendix A, Table 3. Prior office visits were calculated based on observations in the other therapy file and were used as a continuous variable in the analysis. Observations in the other therapy file with place of service codes 11 (office), 22 (outpatient hospital), 71 (state or public health clinic), or 72 (rural health clinic) or procedure codes 99201-99215, 99241-99245, 99354-99355, 99381-99429 were classified as office visits. Prior opioid prescriptions were identified using NDC codes for narcotic analgesics. The presence or absence of a comprehensive sickle cell center in each patient's state of residence was also represented as a binary variable.

Statistical analyses

All statistical analyses were conducted using the Statistical Analysis System (SAS) version 9.4 (SAS Institute Inc., Cary, NC). Means and standard deviations (SD) were reported for count variables and frequencies and percentages were reported for categorical variables. Bivariate analyses were conducted using t-tests for count predictors, while chi-square tests were

used for comparing categorical predictors between HU users and non-users. Predictors of HU use among patients with SCD were assessed using a logistic regression model (PROC LOGISTIC) with age, gender, race, SCD severity, prior blood transfusions, prior opioid prescriptions, prior office visits, and presence of a comprehensive sickle cell center in the state of residence as independent variables, and use of HU as the dependent variable.

RESULTS

A total of 12,213 beneficiaries in calendar year 2006 met our inclusion criteria. Of these, 1,309 SCD patients (10.72%) were identified as HU users in 2007 (Appendix B, Table 1).

Results for univariable analyses between predictors and HU use conducted using t-tests and chi square tests are presented in Appendix B, Table 2. T-tests revealed significant relationships between age and no. of office visits, and HU use. Users of HU were significantly older ($p<0.0001$), had a greater number of office visits ($p<0.0001$), and used a greater number of opioid prescriptions ($p<0.0001$) compared to non-users. Significant relationships using chi square tests were found between all categorical variables in the model and HU use. Non-black race ($p<0.0001$), male gender ($p = 0.0005$), previous office visit ($p<0.0036$), previous blood transfusion ($p<0.0001$), prior opioid visit ($p<0.0001$), severe disease ($p<0.0001$), and presence of a comprehensive sickle cell center in the same state ($p<0.0001$) were all associated with increased HU use.

The multi-variable model assessing predictors of HU use revealed interesting insights (Appendix B, Table 3). As age increased by one year, the odds of using HU increased by 12% (Odds ratio (OR): 1.12; 95% Confidence Interval (CI): 1.11 - 1.14). Black patients were significantly less likely to use HU compared to patients belonging to other races (OR: 0.73; 95% CI: 0.65 - 0.83). Males were 1.22 times more likely to use HU compared to females (95% CI: 1.08 - 1.37). Disease severity emerged as the strongest predictor of HU use. Patients with severe disease were more likely to use HU compared to those with less severe disease (OR: 2.16;

95% CI: 1.90 - 2.45). Patients with a comprehensive sickle cell center in the same state as their residence were 1.61 times more likely to use HU compared to those without such a center in their state (95% CI: 1.42 - 1.82). As prior office visits increased by one, the odds of using HU increased by 1% (95% CI: 1.01 – 1.02). Patients who had a previous prescription for opioids had a higher likelihood of being an HU user compared to patients who did not use opioids (OR: 2.07; 95% CI: 1.80 – 2.39).

In summary, our results indicate that utilization of HU in the pediatric population with SCD enrolled in Medicaid is low (10.72%). Older age, non-Black race, Male gender, severe disease, presence of a comprehensive sickle cell center in the state of residence, prior opioid use, and prior office visits are all significant predictors of HU use in this population.

DISCUSSION

This study assesses prevalence and predictors of HU use in the pediatric Medicaid population with sickle cell disease. The 2006-2007 Medicaid analytic extract (MAX) files for 40 US states (all US states except Hawaii, Montana, Pennsylvania, Utah, Wisconsin, Washington DC, Wyoming, Alaska, Missouri, North Dakota, and South Dakota) were used for this study. Demographic and health-related predictors were evaluated.

Our study found that the prevalence of HU use among children enrolled in Medicaid in 40 US states was 10.72%. Results of previous studies reporting HU use in adults range from 30% in the Maryland Health Services Cost Review Commission database to 38% and 14% in Florida Medicaid and Maryland Medicaid respectively.[10–12] Since HU is approved for use in adults with SCD, it is not surprising that studies conducted in this population reported substantially more use compared to our study.

The prevalence rate for HU use found in our study is more closely aligned with previous observational research involving pediatric patients. A 2011 study by Tripathi et al. using 1996-2006 South Carolina Medicaid administrative claims reported that only 8.0% children enrolled with SCD received HU treatment.[15] The only other study assessing HU use in children found that 38% children with SCD were on HU therapy.[13] However, this study included self-reported data, which suffers from the inherent limitation of self-report bias, which may be a reason for the reported high rates of medication use.[26]

Our study found that HU use increased with age. Although ours is the first study aimed at specifically testing predictors of HU use in the pediatric population, previous observational studies conducted in the adult population have reported higher use of HU among younger patients.[11,12] For example, Lanzkron et al., whose analysis included five years of de-identified data (2001–2005) from a local managed care organization (MCO), Priority Partners MCO, serving the needs of patients on medical assistance in the State of Maryland found that that HU use was higher among younger as compared to older adults (mean age: 28 years vs. 32 years, p=0.02).[12] Ritho et al. also reported in their study using the Florida Medicaid claims that the mean age of HU users was lower than non-users.[11] HU use has been shown to be associated with cardiovascular, hepatic, renal, and pulmonary complications.[15] A previous study conducted by surveying members of the American Society of Pediatric Hematology/Oncology, it was found that patient's anticipation of side-effects and patient's young age were two of the top five barriers in prescribing HU among pediatric patients.[17] It is not surprising that the trend seen in our study was not similar to that seen in previous studies conducted in the adult population, as the safety of HU in very young pediatric patients is still a major concern among prescribers and patients. Black patients showed a lower likelihood of using HU compared to the other non-Black races. Previous research shows that unmet prescription needs is a prevailing problem among African-American children in the United States.[27] A study conducted with a view to understand factors that influence differences in asthma medication use among children found that African-American children received fewer asthma medications compared to their White counterparts.[28] Although our study was the first one to report that black children with SCD have a lower likelihood of receiving HU, our results are supported by a similar trend seen in other diseases highly prevalent in children. Our study also found that males have a higher likelihood of using

HU compared to females. This finding is consistent with the Lanzkron et al. study conducted in the adult SCD population (males: 22% vs. females: 12%, p=0.01).[12]

Health-related predictors of HU use evaluated in this study were SCD severity, prior blood transfusions, prior office visits, prior opioid prescriptions, and presence of a comprehensive sickle cell center in the state of residence. Disease severity emerged as a significant predictor of HU use wherein patients with severe disease had a higher likelihood of using HU compared to those with less-severe disease (OR: 2.65; 95% CI: 2.34 - 2.99). Although HU is not approved for use in the pediatric population, guidelines published by the NHLBI state that HU is indicated for children (after consultation with parents and expert pediatricians) with SCD experiencing frequent pain episodes, history of acute chest syndrome, or severe symptomatic anemia.[8] Our study provides evidence to suggest that a majority of physicians follow these guidelines when initiating HU treatment in pediatric patients with SCD. Prior opioid use significantly predicted HU use in the pediatric population with SCD. Patients who had a prior opioid prescription were significantly more likely to use HU compared to those who did not use opioids. This finding suggests that prior opioid use is an indicator of disease severity, and patients with greater opioid use are sicker, and in need of HU. Prior office visits were also found to be a significant predictor of HU use in our study. Our results are in accordance with a previous study which reported that HU users had significantly more clinic visits during the preceding 12 months compared to non-users ($p<0.0001$).[13] A positive relationship between prior office visits and HU use is logical considering that greater office visits can be an indication of disease severity, and physicians take this into account when prescribing HU to pediatric patients with SCD.[8] Patients who had a comprehensive sickle cell center within the state of residence had a higher likelihood of using HU for their SCD compared to those who

did not. A previous study by Shankar et al. conducted with a view to assessing the impact of proximity of residence to a comprehensive sickle cell center on medical care utilization and mortality failed to demonstrate a relationship between the two.[22] However, presence of a comprehensive sickle cell center within close proximity is a measure of better access to care, which is why it is not surprising that it has a positive impact on HU use.

Our study has several strengths. First, this is an observational study conducted using Medicaid data from 40 US states, which has the advantage of being representative of the real-world national Medicaid population with the disease. Previous studies that have attempted to do so have used Medicaid data from a single state, the results of which cannot be generalized to the national Medicaid population due to state-to-state differences.[10–12] Second, our study is the first of its kind to assess the prevalence and predictors of HU use in the pediatric population. A number of previous studies with the same goal have been conducted in the adult population.[10–13,16,21] Since HU is not approved for use in the pediatric population, monitoring its use in these patients is of utmost importance. Our study provides evidence to suggest that physicians treating children with SCD follow guidelines that have been put in place for the effective use of HU in this population, and prescribe it mainly to patients with severe disease.

Our study also has a fair share of limitations. First, we used at least three prescription fills in a period of six months as a measure of HU use. However, there is no way of knowing whether HU users continued taking the medication after those three fills, for how long they took the medication while in the study period, and what the reasons for discontinuation were. Second, we tested presence of a comprehensive sickle cell center within the state of residence as one of the predictors of HU use demonstrating access to care. A better measure would be distance from

the nearest comprehensive sickle cell center, since the nearest center for some patients could be in an adjoining state.

In summary, the prevalence of HU use in pediatric patients enrolled in Medicaid was found to be low. This is an indication that physicians are cautious when prescribing HU in children, a population in which HU is not approved for use. Predictors of HU use in the pediatric Medicaid population span from demographic variables (including age, gender, and race) to health-related predictors (including disease severity, previous office visits, prior opioid prescriptions, and presence of a comprehensive sickle cell center within the state of residence). Health-related predictors that were indicators of severe disease (disease severity, prior office visits, and prior opioid prescriptions) were found to positively affect HU use which is a testament to the fact that on average, physicians follow guidelines from agencies such as NIH and NHLBI recommending that HU should only be used in children with severe form of the disease. Future research should examine the clinical and economic outcomes associated with the use of HU in this population.

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LIST OF APPENDICES

APPENDIX A – IDENTIFICATION CODES

Table 1: ICD-9-CM codes for sickle cell disease

ICD-9-CM* code	Description
282.41	Sickle-cell thalassemia without crisis
282.42	Sickle-cell thalassemia with crisis
282.6	Sickle-cell disease
282.60	Sickle-cell disease, unspecified
282.61	Hb-SS disease without crisis
282.62	Hb-SS disease with crisis
282.63	Sickle-cell/Hb-C disease without crisis
282.64	Sickle-cell/Hb-C disease with crisis
282.68	Other sickle-cell disease without crisis
282.69	Other sickle-cell disease with crisis

*ICD-9-CM: International Classification of Diseases, 9th Revision, Clinical Modification

Table 2: NDC codes for hydroxyurea

NDC code	Trade name	Strength
0003-0830	Hydrea capsules	500 mg/1
0003-6335	Droxia capsules	200 mg/1
0003-6336	Droxia capsules	300 mg/1
0003-6337	Droxia capsules	400 mg/1
68084-284	Hydroxyurea capsules	500 mg/1
0555-0882	Hydroxyurea capsules	500 mg/1
49884-724	Hydroxyurea capsules	500 mg/1
54868-4773	Hydroxyurea capsules	500 mg/1
54868-4773	Hydroxyurea capsules	500 mg/1
54868-4773	Hydroxyurea capsules	500 mg/1
54868-4773	Hydroxyurea capsules	500 mg/1
54868-4773	Hydroxyurea capsules	500 mg/1
60429-265	Hydroxyurea capsules	500 mg/1

NDC = National drug classification; mg/l =milligrams per liter.

Table 3: CPT-4, HCPCS procedure, and revenue codes for blood transfusion

Code type	Code	Description
CPT-4	36450	Exchange transfusion, blood; new born
CPT-4	36455	Exchange transfusion, blood; other than new born
CPT-4	36520	Erythrocytapheresis
CPT-4	36521	Erythrocytapheresis
CPT-4	36512	Therapeutic apheresis for red blood cells
HCPCS	P9010	Blood (whole), for transfusion, per unit
HCPCS	P9016	Red blood cells, leukocytes reduced, each unit
HCPCS	P9021	Red blood cells, each unit
HCPCS	P9022	Red blood cells, washed, each unit
HCPCS	P9038	Red blood cells, irradiated, each unit
HCPCS	P9039	Red blood cells, deglycerolized, each unit
HCPCS	P9040	Red blood cells, leukocytes reduced, irradiated, each unit
HCPCS	C1010	Whole blood or red blood cells, leukocytes reduced, CMV-negative, each unit
HCPCS	C1016	Whole blood or red blood cells, leukocytes reduced, frozen, deglycerol, washed, each unit
HCPCS	C1018	Whole blood, leukocytes reduced, irradiated, each unit
Revenue	380	Blood
Revenue	381	Packed red cells
Revenue	382	Whole blood
Revenue	389	Other blood
Revenue	390	Blood storage
Revenue	391	Blood administration
Revenue	399	Other blood storage and processing

CPT-4 = Current procedural terminology 4th edition;
HCPCS = Healthcare common procedure coding system.

APPENDIX B – PREVALENCE AND PREDICTORS OF HYDROXYUREA

Table 4: Prevalence of hydroxyurea use among pediatric patients with sickle cell disease

Hydroxyurea Use	No. of patients	% of patients
Yes	1,309	10.72%
No	10,904	89.28%
Total	**12,213**	

Table 5: Univariable analyses between predictors and hydroxyurea use

Independent variable	HU use		p value
	Yes	No	
Age, Mean (SD)	9.37 (3.63)	6.84 (4.41)	<0.0001
Race			<0.0001
Black	761 (9.46)	7,285 (90.54)	
Non-Black	548 (13.15)	3,619 (86.85)	
Gender			0.0005
Male	744 (11.65)	5,643 (88.35)	
Female	565 (9.70)	5,261 (90.30)	
Office Visit			0.0036
Yes	1,295 (10.84)	10,652 (89.16)	
No	14 (5.26)	252 (94.74)	
No. of office visits, Mean (SD)	16.52 (14.01)	12.04 (13.67)	<0.0001
Disease Severity			<0.0001
Severe	666 (19.17)	2,809 (80.83)	
Not severe	643 (7.36)	8,095 (92.64)	
Prior blood transfusion/s			<0.0001
Yes	381 (15.38)	2,097 (84.62)	
No	928 (9.53)	8,807 (90.47)	
No. of prior blood transfusions, Mean (SD)	0.93 (2.56)	0.92 (3.23)	0.8885
Prior opioid prescription/s			<0.0001
Yes	992 (15.47)	5,420 (84.53)	
No	317 (5.46)	5,484 (94.54)	
No. of prior opioid prescriptions, Mean (SD)	3.26 (4.26)	1.32 (2.48)	<0.0001
Comprehensive sickle cell center in the state of residence			<0.0001
Yes	551 (13.46)	3,542 (86.54)	
No	758 (9.33)	7,362 (90.67)	

HU = Hydroxyurea; SD = Standard Deviation

Table 6: Logistic regression analysis assessing predictors of hydroxyurea use

Independent Variable	Odds Ratio	95% Confidence Interval
Age	1.12	1.11 - 1.14
Race		
Black	0.73	0.65 - 0.83
Non-black	Ref	-
Gender		
Male	1.22	1.08 - 1.37
Female	Ref	-
Disease Severity		
Yes	2.16	1.90 - 2.45
No	Ref	-
Number of Office Visits	1.01	1.01 - 1.02
Prior blood transfusion/s		
Yes	1.10	0.95 - 1.26
No	Ref	-
Prior opioid prescription/s		
Yes	2.07	1.80 - 2.39
No	Ref	-
Comprehensive sickle cell center in the state of residence		
Yes	1.61	1.42 - 1.82
No	Ref	-

CHAPTER 3

PAPER II

IMPACT OF HYDROXYUREA USE ON CLINICAL OUTCOMES AMONG CHILDREN WITH SICKLE CELL DISEASE ENROLLED IN MEDICAID

ABSTRACT

Objectives: Hydroxyurea (HU) is the only treatment approved for use in adults with sickle cell disease (SCD) to decrease clinical complications, mainly sickle cell crises. The goal of this paper was to test the relationship between HU use and crises among pediatric patients with SCD enrolled in Medicaid.

Methods: The cohort for this study comprised of HU-naïve SCD patients in 2006, who were enrolled in the Medicaid program in 40 US states for at least 27 months from calendar year 2006 to 2008 and who were less than 18 years of age as of December 31, 2008. The relationship between HU use and presence of a sickle cell crisis was tested using a matched cohort analysis. HU users from the study cohort were matched with non-users on age and gender (1:1) using a greedy matching algorithm. Presence of a sickle cell crisis in each matched pair was measured from the date of first HU prescription to the end of 2008. The impact of HU use on number of crises was evaluated in the unmatched sample using conventional multivariable analysis and an instrumental variables approach, to control for observed as well as unobserved confounding. HU users from the cohort of SCD patients described previously were identified in calendar year 2007. Number of crises for this entire unmatched sample were then identified in calendar year 2008. Regional variations in HU use at the county level and prescriber's preference for HU were used as instrumental variables in the analysis.

Results: The impact of HU use on presence of a sickle cell crisis in the matched cohort study was found to be non-significant (OR: 1.33; 95% CI:0.78-2.25). Results of the conventional

multivariable regression analysis suggested that HU users had a significantly greater number of crises events compared to non-users (β=0.93; $p<0.0001$). However, upon removing the effect of selection bias using instrumental variables, this relationship became non-significant (β=-2.75; p=0.2013).

Conclusion: The results of our matched cohort analysis failed to corroborate the beneficial effect of using HU in reducing the likelihood of having a crisis in children with SCD reported by previous clinical trials. The findings from the conventional multivariable model stating that HU use may significantly increase the number of crises in children are in accordance with previous observational research, and this disparity between clinical trials and observational studies indicates the presence of selection bias in observational research conducted with this goal. The finding that use of instrumental variables steers the results in the direction of previous clinical trials decreases the validity of previous observational studies that solely control for observed confounding and encourages researchers to take measures to control for unobserved confounding when assessing these relationships.

INTRODUCTION

Approved by the US FDA (Food and Drug Administration) in 1998, hydroxyurea (HU) is used in adult patients with sickle cell disease (SCD) to increase the percentage of fetal hemoglobin in circulation, thus decreasing SCD-related clinical complications, mainly vaso-occlusive events (VOEs).[1,2] Although not approved for use in the pediatric population with SCD, several agencies including the National Institutes of Health (NIH) recommend the use of HU in children who have had three or more severe vaso-occlusive pain events (crises) per year, three or more episodes of acute chest syndrome (ACS) per year, or three or more episodes of any combination of crises and ACS events.[3] The NIH published a consensus statement stating that evidence regarding clinical outcomes of HU therapy differs in adults and children.[4] In adults with SCD, high grade evidence is available regarding the effectiveness of HU to decrease sickle cell crises, while the evidence available in children is moderate. Two systematic reviews, one in the adult population and another in the pediatric population with SCD also agree that current evidence in support of HU to effectively decrease crises events is insufficient, and there is a need of research in this area.[5,6]

The primary evidence for efficacy of HU as a therapeutic agent for SCD was obtained from the Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH) randomized, placebo-controlled clinical trial conducted in 299 adult SCD patients at 21 sites in the United States and Canada.[7] This study found that patients assigned to the HU-treatment group had significantly lower rates of vaso-occlusive crises than the placebo group (median: 2.5 crises vs. 4.5 crises per

year, $p < 0.001$). The median times to the first crisis (3.0 months vs. 1.5 months, $p = 0.01$) and the second crisis (8.8 months vs. 4.6 months, $p < 0.001$) were significantly longer with HU treatment.

The safety and efficacy of HU in children was first established in a multicenter prospective trial of HU by Scott et al. in 1996 involving 15 severely ill SCD patients.[8] Several randomized clinical trials (RCTs) ever since have established the efficacy of HU in reducing clinical complications in children with SCD.[8–13] In a pre-post study by Santos et al., frequency of crises was measured up to one year before and after initiation of HU therapy in 21 pediatric patients with severe SCD.[10] In the period after initiation of HU, rate of crises decreased from 5 per year to 1.81 per year.

All the studies addressing the effect of HU in pediatric patients described so far are clinical trials with limited generalizability due to enrollment of very few patients under controlled environments. Studies conducted using a large generalizable sample and real-world data for HU use in the pediatric SCD population will provide evidence regarding the effectiveness of HU in this population. There are only two retrospective observational studies reporting the impact of HU use on clinical outcomes using South Carolina Medicaid data in SCD children. Stallworth et al. found that compared with the non-HU cohort, HU users had a significantly higher risk of experiencing crises (Relative risk [RR] = 3.32; $p < 0.0001$).[14] Tripathi et al. compared HU users and non-users on cerebrovascular, hepatic, renal, and pulmonary complications while matching the two groups on a host of patient demographic and clinical parameters. They found that the HU-treated group had a significantly higher risk of cardiovascular (odds ratio [OR] = 3.15; confidence interval [CI] = 1.97–5.03), hepatic (OR = 5.41; CI = 3.54–8.27), renal (OR = 5.09; CI = 3.37–7.67), and pulmonary (OR = 4.07; CI =

1.88–8.79) complications compared to the non-HU-treated group.[15] The findings from these studies are contrary to the results of previously described clinical trials regarding the effect of HU therapy in children with SCD. A shortcoming of these studies is the inappropriate measure of baseline disease severity, used as a confounding variable in the analyses. Disease severity was defined as the mean number of sickle cell crises in the baseline period. This measure fails to incorporate episodes of ACS, which is a crucial criterion in determining disease severity for prescribing HU in the pediatric population. Another limitation of these studies is the use of data from a single state, South Carolina, to assess the impact of HU use on clinical outcomes. As a result, these studies lack generalizability and the aforementioned findings can only be limited to the South Carolina Medicaid population.

Candrilli et al. analyzed North Carolina Medicaid claims data for adults and children with SCD and found that adherence to HU therapy (medication possession ratio [MPR] ≥ 0.80) was associated with a decrease in crises (Hazard ratio[HR]: 0.66; $p = 0.013$) in adults.[16] However, adherence to HU therapy was not found to be associated with VOEs among children (HR: 0.732; $p = 0.174$). This may be the result of an extensively long observation period (10 years) used to measure medication adherence which may have biased its measurement. Unlike other chronic medications such as oral hypoglycemic agents, statins, etc., a patient may not be required to be on HU therapy for an extended period of time because of which the calculation of medication adherence for this condition may be difficult. Another limitation of this study was the use of Charlson's comorbidity index (CCI) as a measure of comorbidity which has been validated only to predict mortality in the adult population. Applying it to pediatric patients to study outcomes other than mortality may be inappropriate.

Although the use of HU as a therapeutic agent in adults with SCD has been established based on promising results from several clinical trials, evidence regarding its effectiveness in the pediatric SCD population is mostly inconclusive. Clinical trials showing that HU use results in a decrease in clinical complications of SCD in the pediatric population are extremely small in size with limited generalizability. Observational studies conducted with the same goal have shown the opposite result and have used Medicaid claims data from a single state to assess these relationships in the pediatric SCD population. The NIH supports 10 comprehensive sickle cell centers in the US in states including Texas, North Carolina, California (two), Ohio, NY, Philadelphia (two), Massachusetts, and Tennessee that carry out research on improved treatments for SCD and support activities which incorporate contemporary models of SCD care and treatment into the clinical setting. Hence, results of studies conducted using Medicaid administrative claims data from these states cannot be generalized to the national Medicaid population because presence of comprehensive care centers located in specific states has been shown to have an impact on outcomes among patients with SCD.[17,18]

The population with SCD enrolled in Medicaid is different from the general population. Children with SCD enrolled in Medicaid have greater hospitalizations and ED visits as compared to privately insured children. Despite this, mean expenditures for these events is lower among children enrolled in Medicaid, which may indicate lower average reimbursement.[19] Also, Medicaid beneficiaries are known to have poorer overall health, lower family income, and lower access to prescription drugs compared to the US population.[20] As a result, research is needed to assess the impact of care delivered to Medicaid-enrolled pediatric SCD patients.

An inherent general limitation of retrospective observational studies is the lack of validity due to endogeneity: as individuals present more symptoms of SCD, the probability of receiving

HU is likely to increase. At the same time, patients with more severe SCD are likely to have more clinical complications. Also, prescriber characteristics may affect HU use since the decision to prescribe HU in this population is based on the prescriber's judgment. This is an example of selection bias present in observational studies in which patients receiving treatment may be inherently different from those not receiving treatment. Standard regression techniques can only control for observed differences between the patients who receive treatment, and those who do not by adding them as covariates in the regression model. However, they do not control for confounding that is unobservable to the researcher. A method to minimize unobservable confounding is by using instrumental variables (IVs) that have two properties: First, cause variation in the treatment variable, and second, not affect the outcome measure directly. One can then estimate how much the variation in the treatment variable that is induced by the IV affects the outcome. This variation, known as exogenous variation, is free of endogeneity and identifies the true relationship between the treatment and the outcome. Using methods of IV analysis to control for the presence of selection bias leads to pseudo-randomization that stratifies patients into different likelihoods of receiving treatment and isolates the variation of the effect of treatment on clinical outcomes (effect of interest). This approach has been widely used in previous research, especially in the field of econometrics.[21–23]

The purpose of this study was to assess the effectiveness of HU therapy on clinical outcomes related to SCD in children enrolled in Medicaid programs from 40 US states. Specifically, the impact of HU use on presence of sickle cell crises and the number of sickle cell crises was tested using conventional methods of analysis. The results thus obtained were then compared with those obtained from an instrumental variables approach designed to eliminate selection bias, and make the results more comparable to randomized trials.

METHODOLOGY

Data source

The 2006-2008 Medicaid analytic extract (MAX) files for 40 US states (all US states except Hawaii, Montana, Pennsylvania, Utah, Wisconsin, Washington DC, Wyoming, Alaska, Missouri, North Dakota, and South Dakota) were used for this study. The MAX personal summary file contains person-level demographic and eligibility data for beneficiaries. The MAX inpatient claims file is an event level file with information regarding the admission and discharge dates, International Classification of Diseases, ninth revision, clinical modification (ICD-9-CM) diagnoses codes (up to ten fields), ICD-9-CM current procedural terminology 4th edition (CPT-4) or healthcare common procedure coding system (HCPCS) procedure codes (up to seven fields), and payment amount. The MAX other services file is an outpatient facility visit level file with information regarding physician services, lab/X-ray, clinic services, ICD-9-CM diagnoses codes (up to two fields), and CPT-4 and HCPCS procedure codes (one field), provider identification number, date of service, place of service, and payment amount. Information from outpatient (non-institutional) facilities including outpatient hospital, physicians' office, and emergency department is included in this file. The MAX pharmacy claims file is a prescription level file with information regarding National Drug Classification (NDC) code, prescription dispensed, payment amount, days of supply, quantity dispensed, prescription date, and prescribing physician ID. All these files mentioned above can be linked by a common encrypted beneficiary ID. Approval to conduct this project was sought from the institutional review board (IRB) at the

University of Mississippi. After this, a data use agreement (DUA) was made with CMS through their Research Data Assistance Center (ResDAC).

Patient Identification and Study Design

The cohort for this study comprised of patients with SCD without a prescription of HU (HU-naïve) in 2006, who were enrolled in the Medicaid program for at least 27 months from calendar year 2006 to 2008 and who were less than 18 years of age as of December 31, 2008. Dual eligible beneficiaries were excluded from the study. Also, patients having a diagnosis for conditions including chronic myeloid leukemia (ICD-9-CM code 205.1), polycythemia vera (ICD-9-CM code 238.4), and essential thrombocythemia (ICD-9-CM code 238.71) in the entire study period were excluded from the study.

Calendar year 2006 served as the baseline period for identification of the SCD cohort. Beneficiaries having two or more claims in calendar year 2006 with ICD-9-CM codes presented in the Appendix A, Table 1 in the inpatient claims and the other services files were identified as SCD patients. Among these, HU-naïve patients were defined as those not having a single prescription with NDC codes from Appendix A, Table 2 in 2006. This cohort was followed into calendar year 2007 to identify HU users and non-users.

The relationship between HU use and presence of a sickle cell crisis was tested using the matched cohort analysis. HU users were matched with non-users on age and gender in a ratio of 1:1 using a greedy matching algorithm.[24] A difference of not more than ± 2 years was allowed while matching HU users and non-users on age, while a perfect match was requested for gender. The date of the first HU prescription among HU users was defined as the index date and was

attributed to each corresponding non-user. Clinical outcomes among HU users and non-users were measured in the follow-up period from the HU index date up to December 31, 2008. A diagrammatic representation of the matched cohort study design is provided in Appendix B, Figure 1. The impact of HU use on number of crises was evaluated on the unmatched sample. HU users and non-users from the cohort of SCD patients described previously were identified in calendar year 2007. The second outcome, number of crises, was identified in calendar year 2008 (Appendix B, Figure 2).

Measures

HU users were defined as patients who had at least three prescriptions of HU in a six month period in 2007. Sickle cell crises were measured using ICD-9-CM diagnosis codes 282.62, 282.64, and 282.69 as a primary or secondary diagnosis code in the impatient and other services files.

Confounders including age, gender, race, baseline SCD severity, baseline office visits, prior blood transfusions, prior opioid prescriptions, and presence (or absence) of a comprehensive sickle cell center in the state of residence were included in the analyses. Age was calculated as age at the end of calendar year 2008 and was used as a continuous variable in the analysis. Gender was measured as a categorical variable with categories male and female. Race was used as categorical variable. It was categorized as Black and Non-Black (consisting of White, Hispanic or Latino, Asian, Native Hawaiian, Pacific Islander, American Indian or Alaskan Native, or unknown race). Baseline SCD severity was calculated as a binary variable in calendar year 2006. Based on SCD guidelines for pediatric patients, those with (1) three or more severe VOEs per year, or (2) three or more episodes of ACS per year, or any combination of (1)

and (2) amounting to three or more episodes per year were categorized as having severe disease. All others were classified as having less severe disease. Office visits during the baseline period were used as a proxy for access to care and past healthcare utilization. Office visits were defined as claims in the other services file with place of service codes 11 (office), 22 (outpatient hospital), 71 (state or public health clinic), or 72 (rural health clinic) or procedure codes 99201-99213, 99241-99245, 99354-99355, 99381-99429. Prior blood transfusions was a binary variable which denoted whether the patient underwent a blood transfusion in 2006 (using CPT-4, HCPCS procedure, and revenue codes presented in Appendix A, Table 3. Prior opioid prescriptions were identified using NDC codes for narcotic analgesics. An identifier variable was created for the presence (or absence) of a comprehensive sickle cell center in the state for patients residing in states including California, Ohio, Texas, New York, North Carolina, Massachusetts, and Tennessee.

The instruments used in this study were measured in calendar year 2006. Three instruments were used in this study; two instruments based on regional variations in HU use, and one instrument denoting prescriber preference for prescription of HU. The two instruments representing regional variations in HU use were (1) volume of Medicaid prescription claims for HU as a percentage of the total volume of Medicaid prescriptions for SCD patients and (2) percent volume of HU prescriptions per Medicaid beneficiary with SCD - both at the county level.[a] The rationale for using these instruments is that patients would have a higher probability of receiving HU in counties where HU diffusion was more wide-spread. Similar instruments at the geography - level have previously been used in several studies.[25–29] The third instrument

[a] The instrumental variables were calculated on a sample of children as well as adults with SCD, to ensure that it is truly exogenous and does not directly affect the outcome measure, which is calculated only in the pediatric population.

used in this study was prescriber's preference for HU in the SCD population. Each SCD patient was assigned a primary prescriber who was defined as the prescriber who wrote the maximum number of prescriptions for that patient in calendar year 2007. Number of HU prescriptions prescribed by the primary prescriber in 2006 as a percentage of the total prescriptions prescribed by the prescriber during the same time period was used as the third IV in this study.

Statistical Analysis

Means and standard deviations were reported for count variables and frequencies and percentages were reported for categorical variables. Univariable analysis using the McNemar's test was used to compare the categorical characteristics of the matched sample. Univariable Poisson regressions were conducted in order to compare the distribution of count covariates in the matched sample. Impact of HU use on presence of sickle cell crises while controlling for the effect of covariates including race, disease severity, prior opioid prescriptions, prior blood transfusions, prior office visits, and presence of a comprehensive sickle cell center in the state of residence was assessed using conditional logistic regression stratified on matched pairs (PROC LOGISTIC procedure with a STRATA statement). Univariable analysis using the chi sq. test was conducted to compare the categorical characteristics, while t-tests were used to compare the count characteristics of HU users and non-users in the unmatched sample. A conventional ordinary least squares (OLS) regression using the PROC REG procedure in SAS was used to test the impact of HU use on number of sickle cell crises, while controlling for the effects of covariates including age, gender, race, disease severity, prior opioid prescriptions, prior blood transfusions, prior office visits, and presence of a comprehensive sickle cell center in the state of residence in the unmatched sample. A two stage least squares regression using the PROC SYSLIN procedure in SAS was used to conduct the IV analysis, the estimates of which were

then compared with the conventional multivariable model predicting the impact of HU use on number of sickle cell crises. Statistical Analysis System (SAS) version 9.4 (SAS Institute Inc., Cary, NC) was used for the purposes of data management and statistical analyses in this study.

RESULTS

A total of 238 SCD patients were identified as being HU-naïve in 2006 and were HU users in 2007. These HU users were then matched with non-users (1:1) on age and gender. The characteristics of this matched sample are displayed in Appendix C, Table 4. A higher proportion of HU non-users were African-American compared to the 'other' race category ($p=0.0008$). Compared to non-users, a higher proportion of HU users had a previous blood transfusion ($p<0.0001$), prior opioid use ($p<0.0001$), severe disease ($p<0.0001$), and a comprehensive sickle cell center located in the state of residence ($p<0.0001$). HU users had a significantly higher mean number of opioid prescriptions compared to non-users ($p<0.0001$).

The results for the conditional logistic regression analysis between HU use and the likelihood of having a sickle cell crisis are presented in Appendix C, Table 5. Controlling for the effects of covariates, HU users had a higher likelihood of having a crisis event compared to non-users (OR: 1.33; CI: 0.78-2.25). However, this relationship was not found to be statistically significant.

The relationship between HU use and number of sickle cell crises was assessed on an unmatched sample of 9,461 Medicaid beneficiaries with SCD, of which 235 were HU users.[b] The characteristics of this sample, presented in Table 6 (Appendix C), were in general similar to the matched study sample. HU users were significantly older compared to non-users ($p<0.0001$).

[b] Some patients could not be assigned a primary prescriber for computation of the third IV (prescriber's preference for HU) as they did not have a single prescription in 2007. Also, the primary prescriber for some patients did not write a single prescription in 2006. After excluding these patients, we were left with 9,461 patients who were used in the analysis.

A significantly lower proportion of HU users were black (p=0.0004), while a significantly higherproportion of HU users had a previous blood transfusion (p<0.0001), had a previous opioid prescription (p<0.0001), and had severe disease (p<0.0001). Also, HU users had significantly greater number of prior blood transfusions (p<0.0001), office visits (p=0.0267), and opioid prescriptions compared to non-users (p<0.0001).

The relationship between HU use and number of sickle cell crises was examined using a conventional multivariable model controlling for observed confounding, and an IV model controlling for observed as well as unobserved confounding. It is prudent to ensure that the IVs under consideration are exogenous and explain the variation in the independent variable. As required, all three IVs were correlated with HU use (p <0.0001) (Appendix D, Table 8). Although the IVs did not predict variation in HU use individually (Appendix D, Table 9), they jointly predicted variation in the treatment (F = 20.30; p<0.0001) (Appendix D, Table 10). Lastly, the Hausman test for endogeneity was found to be significant at an alpha level of 0.1 (t=1.76; p=0.078), which provides evidence to suggest that the IVs are exogenous and the IV model is more efficient than the conventional OLS model (Appendix D, Table 11).

A comparison of the conventional OLS model and the IV model is presented in Appendix C, Table 7. Based on the conventional OLS model, after controlling for the effects of covariates, HU use was found to be associated with significantly increased episodes of sickle cell crises compared to non-users (β = 0.93; p=<0.0001). On the other hand, the IV model provided evidence to suggest that HU users tend to have a have lower number of sickle cell crises compared to non-users (β = -2.75). However, this relationship was not found to be statistically significant (p = 0.2013).

DISCUSSION

Our study, which was aimed at assessing the impact of HU use on clinical outcomes in the pediatric population with SCD, was conducted in the Medicaid population of 40 US states. We evaluated the impact of using HU on the likelihood of having a sickle cell crises as well as the number of sickle cell crises.

Our study did not find a significant relationship between HU use and having a crisis event. However, HU use was associated with a greater number of crises events compared to non-users. Previous clinical trials conducted among pediatric patients with SCD have demonstrated the ability of HU in reducing SCD-related events in children.[8–13] However, these studies have been conducted in a controlled setting with very few patients and fail to account for irregularity in the use of HU. Population-based studies have an advantage over clinical trials in that the results obtained from them are more closely aligned with real-world estimates, and medication use in such studies is not monitored in a controlled setting.

Previous population-based observational studies conducted with the same goal have failed to corroborate the positive clinical effects of HU use among pediatric patients with SCD. A study conducted by Stallworth et al. using the South Carolina Medicaid claims found that patients receiving HU experienced severe and frequent episodes of sickle cell crises over time compared to the control group (RR: 3.32; CI: 2.49 – 4.44).[14] Between 60% and 80% of all hospitalizations for children with SCD are known to be pain-related.[30] Lanzkron et al., in their analysis of adult patients with SCD enrolled in a Medicaid managed care organization in

Maryland found that HU users had significantly higher hospital admission rates than non-users (5 vs. 1.5, p = .004).[31] Although the estimates in the matched cohort analysis and the IV analysis failed to reach statistical significance, our study found results in the same general direction.

In the conventional multivariable analysis testing the impact of HU use on number of sickle cell cises, HU use was found to be significantly associated with an increased number of crises ($\beta = 0.93$; $p<0.01$). Contrary to this, in the IV approach, the relationship between HU use and number of crises was found to be negative but statistically non-significant ($\beta = -2.75$; $p=0.20$). The IV approach used in our study is superior to other population-based studies aimed at testing the beneficial effect of HU in reducing clinical outcomes in the pediatric population with SCD. Although it failed to reach statistical significance, controlling for unobserved confounding resulted in a change in directionality of the relationship between HU use and number of crises. The disparity seen in previous clinical trials and population-based studies with respect to the beneficial effect of HU use on outcomes among children with SCD may be the result of presence of unobserved confounding, as these population-based studies fail to account for unobserved confounding which arises due to selection bias. Further minimizing uncontrolled confounding by the use of stronger instrumental variables may provide results in concordance with clinical trials, thus confirming the beneficial effect HU in this population.

Our study has several strengths. Not only is it one of the very few studies assessing the impact of HU use on clinical outcomes among pediatric patients, it is also the first observational study with this goal to be conducted using Medicaid data from 40 US states. This large-scale population-level study has the advantage of providing robust real-world estimates which can be generalized to the national Medicaid population, unlike small, controlled clinical trials and observational studies conducted using Medicaid claims from a single state. This study is also

superior to previous population-based studies that have failed to account for unobserved confounding that may be present in such studies comparing HU users and non-users. Results obtained from the instrumental variables approach were found to be closer to those obtained in previous clinical trials, and challenge the validity of previous observational studies reporting the negative effects of HU use in pediatric patients with SCD.[14,15] Our study suggests that a better study design and robust analyses employed by observational studies in the future can potentially establish the true effect of HU in the pediatric population in which it is not yet FDA approved.

The results of this study must be interpreted with caution. Patients who had three prescriptions of HU within 6 months were defined as users of HU. However, we don't know whether all these patients continued using HU or were adherent to their medications. We tried to overcome this by using 3 filled prescriptions of HU within a period of 6 months to define HU use in this study. We used a period of one year (calendar year 2006) to establish HU naivity in the cohort of SCD patients. However, we cannot be certain that the sub-cohort of HU naïve patients thus obtained is truly HU naïve, as they may have had prescriptions of HU before 2006. However, even if such a scenario persists, it is unlikely that any HU use before 2006 will affect outcomes in 2007 and 2008. Even though the estimates from the instrumental variable approach proposed in this paper are directionally consistent with results from previous clinical trials, the method and results should be interpreted with caution. We used primary prescriber's preference for HU as an instrumental variable in this analysis. While we assigned the prescriber who prescribes the most medications as a patient's primary prescriber, there may be a scenario wherein the primary prescriber is not an SCD expert, and the patient sees a secondary prescriber for his SCD needs. However, this is unlikely considering that children with SCD have primary medical needs related to the disease, and the physician treating them for SCD would most likely

be their primary prescriber. The prescriber IDs used to identify the primary prescriber for each patient in the sample were state-specific. This means that the prescriber's tendency to prescribe HU would be based solely on the patient's state of residence. For example, if patient A's primary provider sees patients from a neighboring state, the prescriptions prescribed to these out-of-state patients will not be counted towards the computation of the prescribing preference-based IV for patient A.

In summary, HU use was not found to be significantly related to having a crisis event among pediatric patients with SCD enrolled in Medicaid. A significant and positive relationship between HU use and the number of sickle cell crises was found in the conventional multivariable model controlling for the effects of observed confounding only. After controlling for the effect of unobserved confounding through the use of IVs, this relationship changed directionality to become negative, but it did not reach statistical significance. Future studies should aim at exploring additional ways to establish the true effects of HU on clinical outcomes among children with SCD at the population level. Effects of HU use on resource utilization and costs associated with SCD in the pediatric population must also be investigated.

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LIST OF APPENDICES

APPENDIX A – IDENTIFICATION CODES

Table 1: ICD-9-CM codes for sickle cell disease

ICD-9-CM* code	Description
282.41	Sickle-cell thalassemia without crisis
282.42	Sickle-cell thalassemia with crisis
282.6	Sickle-cell disease
282.60	Sickle-cell disease, unspecified
282.61	Hb-SS disease without crisis
282.62	Hb-SS disease with crisis
282.63	Sickle-cell/Hb-C disease without crisis
282.64	Sickle-cell/Hb-C disease with crisis
282.68	Other sickle-cell disease without crisis
282.69	Other sickle-cell disease with crisis

*ICD-9-CM: International Classification of Diseases, 9th Revision, Clinical Modification

Table 2: NDC codes for hydroxyurea

NDC code	Trade name	Strength
0003-0830	Hydrea capsules	500 mg/1
0003-6335	Droxia capsules	200 mg/1
0003-6336	Droxia capsules	300 mg/1
0003-6337	Droxia capsules	400 mg/1
68084-284	Hydroxyurea capsules	500 mg/1
0555-0882	Hydroxyurea capsules	500 mg/1
49884-724	Hydroxyurea capsules	500 mg/1
54868-4773	Hydroxyurea capsules	500 mg/1
54868-4773	Hydroxyurea capsules	500 mg/1
54868-4773	Hydroxyurea capsules	500 mg/1
54868-4773	Hydroxyurea capsules	500 mg/1
54868-4773	Hydroxyurea capsules	500 mg/1
60429-265	Hydroxyurea capsules	500 mg/1

NDC = National drug classification; mg/l =milligrams per liter.

Table 3: CPT-4, HCPCS procedure, and revenue codes for blood transfusion

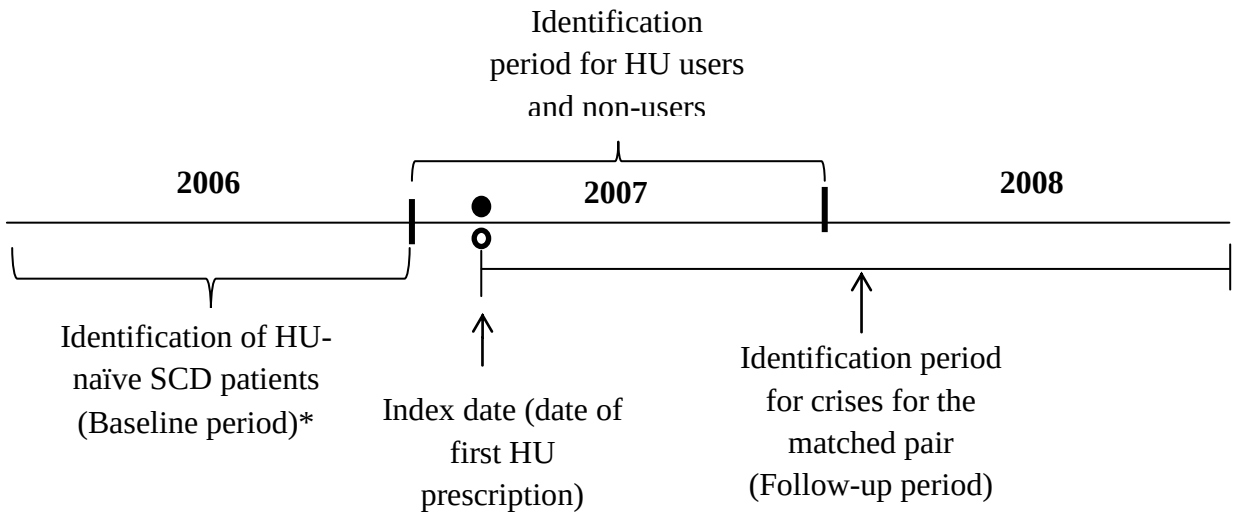
Code type	Code	Description
CPT-4	36450	Exchange transfusion, blood; new born
CPT-4	36455	Exchange transfusion, blood; other than new born
CPT-4	36520	Erythrocytapheresis
CPT-4	36521	Erythrocytapheresis
CPT-4	36512	Therapeutic apheresis for red blood cells
HCPCS	P9010	Blood (whole), for transfusion, per unit
HCPCS	P9016	Red blood cells, leukocytes reduced, each unit
HCPCS	P9021	Red blood cells, each unit
HCPCS	P9022	Red blood cells, washed, each unit
HCPCS	P9038	Red blood cells, irradiated, each unit
HCPCS	P9039	Red blood cells, deglycerolized, each unit
HCPCS	P9040	Red blood cells, leukocytes reduced, irradiated, each unit
HCPCS	C1010	Whole blood or red blood cells, leukocytes reduced, CMV-negative, each unit
HCPCS	C1016	Whole blood or red blood cells, leukocytes reduced, frozen, deglycerol, washed, each unit
HCPCS	C1018	Whole blood, leukocytes reduced, irradiated, each unit
Revenue	380	Blood
Revenue	381	Packed red cells
Revenue	382	Whole blood
Revenue	389	Other blood
Revenue	390	Blood storage
Revenue	391	Blood administration
Revenue	399	Other blood storage and processing

CPT-4 = Current procedural terminology 4th edition;
HCPCS = Healthcare common procedure coding system.

APPENDIX A – RELATIONSHIP BETWEEN HU USE AND CLINICAL OUTCOMES

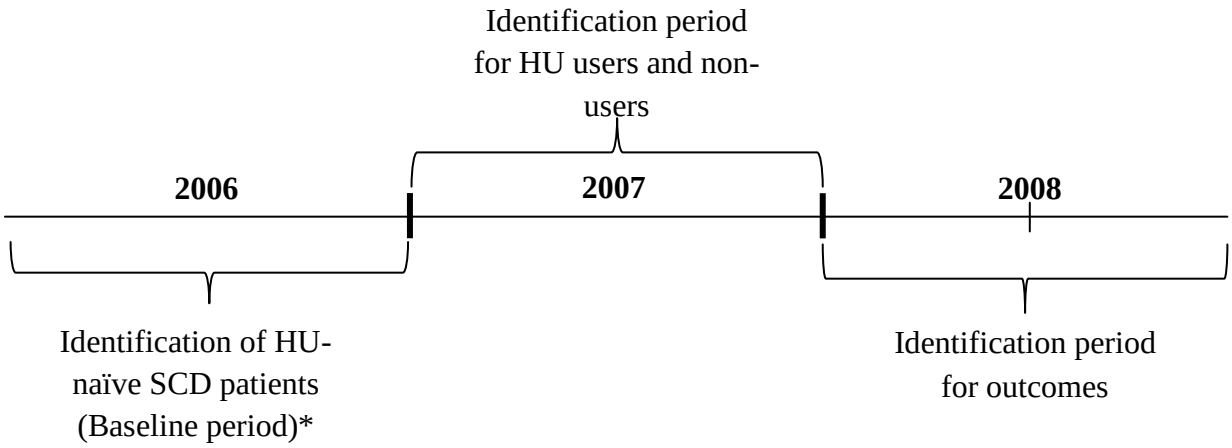
APPENDIX B - FIGURES

Figure 1: Matched cohort analysis to assess the impact of HU use on having a sickle cell crisis



HU: Hydroxyurea
SCD: Sickle cell disease
● : HU user
O : HU non-user matched with the HU user
*Observed covariates were identified in the baseline period.
Note: HU users were defined as HU-naïve SCD patients (identified from calendar year 2006) having 3 prescriptions of HU within 6 months in 2007.
HU non-users were defined as HU-naïve SCD patients (identified from calendar year 2006) who do not have a prescription of HU in 2007.

Figure 2: Analysis using instrumental variables analyzing the relationship between HU use and number of sickle cell crises



HU: Hydroxyurea
SCD: Sickle cell disease
*Identification of observed covariates will also take place in the baseline period.
Note: HU users were defined as HU-naïve SCD patients (identified from calendar year 2006) having 3 prescriptions of HU within 6 months in 2007.
HU non-users will be defined as HU-naïve SCD patients (identified from calendar year 2006) who do have a prescription of HU in 2007.

APPENDIX C – RELATIONSHIP BETWEEN HU USE AND CLINICAL OUTCOMES

Table 4: Characteristics of the matched sample

Characteristic	HU users (N=238)	HU non-users (N=238)	p value
Race			0.0008
Black	132 (55.46)	161 (67.65)	
Non-black	106 (44.54)	77 (32.35)	
Previous blood transfusions			<0.0001
Yes	96 (40.34)	50 (21.01)	
No	142 (59.66)	188 (78.99)	
Comprehensive center in the state of residence			<0.0001
Yes	78 (32.77)	75 (31.51)	
No	160 (67.23)	163 (68.49)	
Previous opioid prescription			<0.0001
Yes	174 (73.11)	123 (51.68)	
No	64 (26.89)	115 (48.32)	
Disease Severity			<0.0001
Yes	129 (54.20)	53 (22.27)	
No	109 (45.80)	185 (77.73)	
No. of previous blood transfusions, Mean (SD)	1.60 (3.27)	1.28 (4.01)	0.3606
No. of previous office visits, Mean (SD)	14.20 (11.30)	12.24 (16.94)	0.1739
No. of previous opioid prescriptions, Mean (SD)	2.69 (3.03)	1.26 (2.01)	<0.0001

HU = Hydroxyurea; SD = Standard Deviation

Table 5: Conditional logistic regression analysis demonstrating the relationship between hydroxyurea use and having a sickle cell crisis event

Independent variable	Odds Ratio	Confidence Interval
HU use		
Yes	1.33	0.78 - 2.25
No	Ref	-
Race		
Black	0.32	0.14 - 0.73
Non-Black	Ref	-
Previous blood transfusions		
Yes	1.87	0.71 - 4.93
No	Ref	-
Previous opioid prescription		
Yes	1.22	0.58 - 2.57
No	Ref	-
Disease severity		
Yes	2.97	1.31 - 6.77
No	Ref	-
Number of previous office visits	1.00	0.96 - 1.04
Comprehensive center in the state of residence		
Yes	0.78	0.36 - 1.70
No	Ref	-

HU = Hydroxyurea; Ref = Reference category

Table 6: Characteristics of the unmatched sample for analysis using instrumental variables

Characteristic	HU users (N=235)	HU non-users (N=9,226)	p value
Age	8.01 (4.03)	6.70 (4.36)	<0.0001
Gender			0.4522
Male	127 (54.04)	4,757 (51.56)	
Female	108 (45.96)	4,469 (48.44)	
Race			0.0004
Black	130 (55.32)	6,130 (66.44)	
Non-black	105 (44.68)	3,096 (33.56)	
Previous blood transfusions			<0.0001
Yes	93 (39.57)	1,785 (19.35)	
No	142 (60.43)	7,441 (80.65)	
Comprehensive center in the state of residence			0.7756
Yes	78 (33.19)	2,981 (32.31)	
No	157 (66.81)	6,245 (67.69)	
Previous opioid prescription			<0.0001
Yes	172 (73.19)	4,682 (50.75)	
No	63 (26.81)	4,544 (49.25)	
Disease Severity			<0.0001
Yes	127 (54.04)	2,339 (25.35)	
No	108 (45.96)	6,887 (74.65)	
No. of previous blood transfusions, Mean (SD)	1.57 (3.27)	0.99 (3.41)	0.0075
No. of previous office visits, Mean (SD)	14.20 (11.36)	12.51 (14.02)	0.0267
No. of previous opioid prescriptions, Mean (SD)	2.63 (2.87)	1.31 (2.38)	<0.0001

HU = Hydroxyurea; SD = Standard Deviation

Table 7: Comparison of estimates from the conventional multivariable model and the instrumental variable model

	Conventional OLS Regression		Instrumental Variable Analysis	
Independent variable	**Estimate**	**p value**	**Estimate**	**p value**
HU use				
Yes	0.93	<0.0001	-2.75	0.2013
No	Ref		Ref	
Age	0.03	<0.0001	0.03	<0.0001
Gender				
Female	0.11	0.0328	0.10	0.0489
Male	Ref		Ref	
Race				
Black	-0.04	0.4467	-0.08	0.2091
Non-black	Ref		Ref	
Previous blood Transfusions				
Yes	0.49	<0.0001	0.57	<0.0001
No	Ref		Ref	
Comprehensive center in the state of residence				
Yes	0.03	0.5973	0.03	0.5494
No	Ref		Ref	
Previous opioid prescription				
Yes	0.66	<0.0001	0.71	<0.0001
No	Ref		Ref	
Disease Severity				
Yes	1.45	<0.0001	1.56	<0.0001
No	Ref		Ref	
No. of previous office visits	0.01	0.6102	0.01	0.6810

HU = Hydroxyurea; OLS = Ordinary least squares regression

APPENDIX D – TESTING ASSUMPTIONS OF INSTRUMENTAL VARIABLES

Table 8: Pairwise correlations between hydroxyurea use and the instrumental variables

	HU use	IV 1	IV 2	IV 3
HU use r (p value)	1.00000			
IV 1 r (p value)	0.043 (<0.0001)	1.00000		
IV 2 r (p value)	0.040 (0.0001)	0.895 (<0.0001)	1.00000	
IV 3 r (p value)	0.072 (<0.0001)	0.212 (<0.0001)	0.214 (<0.0001)	1.00000

Table 9: First stage regression demonstrating whether instrumental variables predict variance in the independent variable - Test of joint significance

Source	DF	F Value	p value
Numerator	3	20.30	<.0001
Denominator	9,449		

Table 10: First stage regression demonstrating whether instrumental variables predict variance in the independent variable - Test of individual significance

Variable	Parameter Estimate	t value	p value
Age	0.001	2.64	0.008
Sex			
Female	-0.002	-0.63	0.526
Male			
Race			
Black	-0.009	-2.69	0.007
Non-Black			
Disease severity			
Yes	0.028	7.24	<.0001
No			
Comprehensive sickle cell center in the state of residence			
Yes	-0.001	-0.15	0.877
No			
Number of previous office visits	-0.000	-0.11	0.909
Previous blood transfusion			
Yes	0.022	5.33	<.0001
No			
Previous opioid prescription			
Yes	0.012	3.69	0.0002
No			
IV 1	0.002	1.24	0.217
IV 2	0.001	0.21	0.836
IV 3	0.002	6.32	<.0001

Table 11: Hausman test for endogeneity

Variable		Estimate	t Value	p value
HU use				
	Yes	-2.747	-1.31	0.190
	No			
Age		0.030	4.65	<.0001
Sex				
	Female	0.105	2.02	0.044
	Male			
Race				
	Black	-0.075	-1.29	0.198
	Non-Black			
Disease severity				
	Yes	1.556	18.19	<.0001
	No			
Comprehensive sickle cell center in the state of residence				
	Yes	0.034	0.61	0.539
	No			
Number of previous office visits		0.001	0.42	0.673
Previous blood transfusion				
	Yes	0.571	6.95	<.0001
	No			
Previous opioid prescription				
	Yes	0.705	11.55	<.0001
	No			
Residuals		3.701	1.76	0.078

CHAPTER 4

PAPER III

HYDROXYUREA USE AND ECONOMIC OUTCOMES AMONG CHILDREN WITH SICKLE CELL DISEASE ENROLLED IN MEDICAID

ABSTRACT

Introduction: The objective of this study was to examine the impact of hydroxyurea (HU) on economic outcomes in pediatric patients with sickle cell disease (SCD) enrolled in Medicaid. The goal of this paper is to test whether the beneficial effects of using HU demonstrated in previous clinical trials translate into decreased resource utilization and healthcare costs at the population-level.

Methods: This was a retrospective matched cohort study conducted in a sample of HU-naïve SCD patients in 2006 enrolled in Medicaid programs from 40 US states. The inclusion criteria for this study was enrollment in Medicaid for at least 27 months from calendar year 2006 to 2008, age less than 18 years of age as of December 31, 2008, and non-dual eligibility. HU users (patients with at least three fills of HU in a period of 6 months) from the study cohort were identified in 2007 and were matched with non-users on age and gender (1:1) using a greedy matching algorithm. The first date of HU prescription (index date) for each HU user in the matched pair was assigned to the corresponding non-user. Economic outcomes including presence of hospitalizations and emergency department (ED) visits, length of stay (LOS), and medical costs in each matched pair were measured from the index date to the end of 2008.

Results: 238 HU users were matched to an equal number of non-users. HU users were significantly more likely to have a hospitalization event (OR: 2.09; CI: 1.28 – 3.43) compared to non-users. This group also reported a significantly longer LOS (β: 0.49; CI: 0.14 – 0.84).

Conclusions: Healthcare providers caring for pediatric patients with SCD should weigh the benefits and risks associated with HU use before prescribing it in this population. Most clinical trials have reported the beneficial effects of HU use on resource utilization in children more than one or two years after the initiation of HU therapy. Future observational studies should aim at assessing the impact of HU use on long-term resource utilization in pediatric patients.

INTRODUCTION

Sickle cell disease (SCD) is a chronic blood disorder affecting approximately 90,000 Americans.[1] Overall, the life expectancy for patients with SCD is 42 years in men and 48 years in women.[2] In their lifetime, SCD patients may suffer from complications including painful vaso-occlusive events (VOEs) more commonly known as sickle cell crises, episodes of acute chest syndrome (ACS), stroke, priapism, and infections.[3] SCD also significantly affects the quality of life of patients and caregivers.[4,5] As a result of its clinical and psychological manifestations, SCD is associated with a significant economic burden.

Although not approved by the FDA in pediatric patients, research has demonstrated that hydroxyurea (HU) can reduce crises, episodes of ACS, and stroke among other symptoms of SCD in adults as well as in children.[6–11] As a result, several agencies and organizations including the National Institutes of Health (NIH) have recommended the use of HU in treating children with severe SCD.

Previous studies indicate that SCD imposes a significant healthcare burden on patients. A study by Brousseau et al. found that publicly insured adults with SCD have almost five hospital encounters per patient per year. The re-hospitalization rates for patients with SCD were also found to be high; 33.4% for 30-day rehospitalizations and 22.1% for 14-day rehospitalizations.[12] Another study reported that SCD patients accounted for approximately 8,400 hospital admissions and more than $59 million in hospital charges in the two-year duration from 1992 to 1993.[13] Since SCD is a condition with significant economic burden, it is important

to demonstrate improvement in economic outcomes such as healthcare resource utilization and costs associated with the use of HU.

Evidence from studies conducted in the adult population suggests that use of HU significantly reduces healthcare resource utilization and costs in adults with SCD. Moore et al. analyzed data from the Multicenter Study of Hydroxyurea (MSH) trial involving adult patients with SCD in the United States and Canada.[14] The total annual average cost per patient receiving HU was $16,810 while that for the non-HU group was $22,020. Although this difference was not statistically significant (p = 0.21), cost for hospitalizations due to vaso-occlusive crises was significantly higher in the non-HU cohort as compared to the HU cohort (p = 0.048). Ferguson et al. examined computerized medical records of 60 adults with SCD who had received HU treatment for at least 3 months in Maryland and Washington, D.C.[15] There was a significant decline in the average number of hospitalizations per patient per year after beginning HU therapy (0.825 hospital admissions vs. 0.52 hospital admissions per year; p = 0.04). Candrilli et al. assessed economic outcomes of HU adherence in children and adults with SCD using the North Carolina Medicaid claims data.[16] It was found that adherence to HU therapy (medication possession ratio [MPR] > 80%) was associated with a reduced risk of SCD-related hospitalizations (hazard ratio [HR] = 0.65; p = 0.0351) and all-cause emergency department (ED) visits (HR = 0.72; p = 0.0388), and a significant reduction in total healthcare costs (-$6,529; p<0.0001). Adherence to HU was also associated with significant reductions in all-cause inpatient costs, ancillary care costs, and vaso-occlusive event-related costs (p < .0001).

A few studies have assessed the impact of HU use on economic outcomes such as healthcare resource utilization and costs in pediatric patients with SCD. The Belgian registry is a national registry of SCD patients (children and young adults) treated with HU which was

initiated in 1998. Ferster et al. used data from the Belgian registry to compare rate of hospitalizations before and after initiation of HU therapy among 22 children with SCD.[17] Number of hospitalizations ($p = 0.0002$) and length of hospital stay ($p < 0.0001$) were significantly higher before initiation of HU and reduced one year after initiation of therapy. In a more recent study using the same data, Gulbis et al. found similar results.[18] Scott et al. administered HU to 10 children with severe SCD in a multicenter, prospective trial to compare the effect of HU use on hospitalization rate.[19] At the end of one year of HU treatment it was found that median number of hospitalizations decreased from 4.1 ± 2.2 days per month before HU initiation to 1.0 ± 1.7 days per month after HU initiation ($p = 0.03$). In a sub-analysis from the study conducted using North Carolina Medicaid claims, it was found that patients adherent to HU had significantly lower costs for all-cause inpatient visits ($4,755 vs. $6,750; $p < 0.0001$), ED visits ($204 vs. $515; $p < 0.0001$), and total costs ($10,140 vs. $13,658; $p < 0.0001$) as compared to non-adherent patients. Costs for pharmacy services were found to be higher among patients adherent to HU therapy ($1,246 vs. $1,041; $p < 0.025$); however, this is expected considering that higher adherence will result in higher pharmacy costs.[20]

A drug's effectiveness is further supported when it can produce economic savings at the population level. Medicaid is the largest health insurer in the US providing coverage to almost 50 million people.[21] Medicaid beneficiaries have poorer overall health, lower family income, and lower access to prescription drugs compared to the US population.[22] Also, children with SCD enrolled in Medicaid have greater hospitalizations and ED visits as compared to privately insured children.[23] As a result, it is of importance to assess the relationship between HU use and economic outcomes in this population. The previously discussed results from the Candrilli study in children enrolled in North Carolina Medicaid cannot be generalized to the national Medicaid

population due to presence of a comprehensive care center and differences in policy as compared to other states. The present study aims to demonstrate the relationship between HU use and economic outcomes in the pediatric SCD population enrolled in Medicaid programs nationwide. The purpose of this study is to examine the impact of HU use on health services utilization including hospitalizations, ED visits, length of hospital stay, and health care costs in pediatric SCD patients enrolled in Medicaid programs in 40 US states.

METHODOLOGY

Data source

The 2006-2008 Medicaid analytic extract (MAX) files for 40 US states (all US states except Hawaii, Montana, Pennsylvania, Utah, Wisconsin, Washington DC, Wyoming, Alaska, Missouri, North Dakota, and South Dakota) were used for the purpose of this study. Medicaid eligibility, inpatient claims, medical claims, and pharmacy claims MAX files were used in this study. The MAX personal summary file contains person-level demographic and eligibility data for all Medicaid beneficiaries. The MAX inpatient claims file is an event level file containing information regarding the admission and discharge dates, diagnoses, and payment amount. The MAX other services file is an outpatient facility (outpatient hospital, physician office, ED) visit level file with information regarding physician services, diagnoses, provider identification number (ID), and payment amount. The MAX pharmacy claims file is a prescription level file containing information regarding National Drug Classification (NDC) code, prescription dispensed, payment amount, days of supply, quantity dispensed, prescription date, and prescribing physician ID. All these files can be linked by a common encrypted beneficiary ID. Approval to conduct this project was sought from the institutional review board (IRB) at the University of Mississippi. After this, a data use agreement (DUA) was made with the CMS through their Research Data Assistance Center (ResDAC).

Patient identification

The cohort for this study comprised of SCD patients without a prescription of HU in 2006 (HU-naïve), who were enrolled in Medicaid for at least 18 months in calendar years 2007-2008, less than 18 years of age as of December 31, 2008, and who were not dual-eligibles. Patients with conditions including chronic myeloid leukemia (International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) code 205.1), polycythemia vera (ICD-9-CM code 238.4), and essential thrombocythemia (ICD-9-CM code 238.71) were excluded from the study.

Presence of SCD was defined as having at least two medical claims for SCD (Appendix A, Table 1) in calendar year 2006. HU-naïve patients were defined as those not having a single HU prescription identified by NDC codes presented in Appendix A, Table 2, in 2006. This cohort was followed into calendar years 2007 and 2008 to determine HU use and outcomes.

Measures

HU users were defined as patients who had at least three prescriptions of HU within 6 months in calendar year 2007. The date of first HU prescription was identified as the index date. Outcomes including hospitalizations, length of hospital stay, and ED visits were measured in the follow-up period (period after the index date) and were disease-specific. Medical costs were identified from the personal summary file and represented all-cause costs in the form of amount paid by Medicaid as reimbursements. Hospitalizations were defined as all events in the inpatient file with an ICD-9-CM code for SCD (Appendix A, Table 1) as the primary or secondary diagnosis. Length of hospital stay was calculated as number of days from the hospital admission date to the discharge date for all patients having a hospitalization. In the event that a patient had

multiple hospital admissions, the lengths of all the hospital stays were added to obtain a cumulative length of hospital stay. ED visits were defined as events with place of service code 23 in the other therapy file and those with revenue codes of 450-459 or procedure codes 99281-99285 in the other therapy or inpatient files with a primary or secondary diagnosis code for SCD (Appendix A, Table 1). Since the perspective of this study was Medicaid, medical costs were defined as amount reimbursed by Medicaid for services related to SCD (primary or secondary diagnosis code in Appendix A, Table 1) from the inpatient and other services file.

Confounders including age, gender, race, baseline SCD severity, baseline office visits, prior blood transfusions, prior opioid prescriptions, and presence (or absence) of a comprehensive sickle cell center in the state of residence were included in the analyses. Age was calculated as age at the end of calendar year 2008 and was used as a continuous variable in the analysis. Gender was measured as a categorical variable with categories male and female. Race was used as categorical variable and was categorized as Black and non-Black (including White, Hispanic or Latino, Asian, Native Hawaiian, Pacific Islander, American Indian or Alaskan Native, or unknown race). Baseline SCD severity was calculated as a binary variable in calendar year 2006. Based on SCD guidelines for pediatric patients, those with (1) three or more severe vaso-occlusive pain events per year, OR (2) three or more episodes of acute chest syndrome per year, OR any combination of (1) and (2) amounting to greater than two episodes per year were categorized as having severe disease.[24] All others were classified as having less severe disease. Baseline office visits were defined as claims in the other services file with place of service codes 11 (office), 22 (outpatient hospital), 71 (state or public health clinic), or 72 (rural health clinic) or procedure codes 99201-99215, 99241-99245, 99354-99355, 99381-99429. Prior blood transfusions were a binary variable which will denote whether the patient underwent a blood

transfusion in 2006 (using CPT-4, HCPCS procedure, and revenue codes presented in Appendix A, Table 3. Prior opioid prescriptions were identified using NDC codes for narcotic analgesics. An identifier variable was created for the presence (or absence) of a comprehensive sickle cell center in the state for patients residing in states including California, Ohio, Texas, New York, North Carolina, Massachusetts, and Tennessee.

Study Design

This was a retrospective longitudinal matched cohort study. HU users identified in 2007 were matched with non-users on age and gender in a ratio of 1:1 using a greedy matching algorithm.[25] The index date for each HU user was attributed to the corresponding non-user. Resource utilization outcomes for each pair were identified from the index date to the end of 2008.

Statistical analysis

HU use was the categorical independent variable; presence or absence of an SCD-specific hospitalization, length of hospital stay, presence or absence of an SCD-specific ED visit, and medical costs were dependent variables; and race, baseline SCD severity, baseline office visits, prior blood transfusions, prior opioid prescriptions, and presence of a comprehensive sickle cell center in the state of residence were confounding variables. Means and standard deviations were reported for continuous variables and frequencies and percentages were reported for categorical variables. Univariable analyses on the matched sample were conducted using McNemar's test for categorical variables and paired t-tests were used for count variables in order to compare the distribution of covariates and outcomes between HU users and non-users. Categorical outcomes including hospitalizations and ED visits were analyzed using separate conditional logistic

regression models to determine the impact of HU use on the likelihood of having a hospitalization and an ED visit. Multivariable analyses using conditional Poisson regressions stratified on matched pairs were used for length of hospital stay. Since costs are not likely to be normally distributed, the sample distribution was identified using the modified Park's test. Generalized linear model (GzLM) with a log link and the appropriate distribution were then used to determine the impact of HU use on medical costs.[a] Data analyses were performed using Statistical Analysis System (SAS) version 9.4 (SAS Institute Inc., Cary, NC).

[a] Because we had a matched ample, costs in the GzLM were annualized so as to be comparable from one person to another.

RESULTS

238 patients were identified as being HU-naïve in 2006 and were HU users in 2007. To account for the potential disparity in HU users and non-users, a sample matched on age and gender (1:1) was created. The characteristics of this matched sample are displayed in Appendix B, Table 4. A higher proportion of HU non-users were Black compared to HU users ($p=0.0008$). Compared to non-users, a higher proportion of HU users had a previous blood transfusion ($p<0.0001$), used opioids ($p<0.0001$), had severe disease ($p<0.0001$), and had a comprehensive sickle cell center within the state of residence ($p<0.0001$). HU users had a significantly greater number of opioid prescriptions compared to non-users ($p<0.0001$).

Univariable analysis revealed a significant inverse relationship between HU use and hospitalizations, ED visits, and LOS (Appendix B, Table 5). A significantly greater proportion of HU users had a hospitalization event compared to non-users ($p=0.0035$). Similarly, a significantly greater proportion of HU users had an ED visit compared to non-users ($p<0.0001$). The mean length of stay for HU users (17.78 days) was significantly greater than non-users (6.36 days) ($p<0.0001$). Also, HU users had significantly greater mean costs compared to non-users ($p<0.0001$).

Multivariable analyses between HU use and outcomes representing resource utilization including hospitalizations, ED visits, and LOS are presented in Appendix B, Tables 6, 7, and 8 respectively. Controlling for the effect of covariates, HU users were significantly more likely to have an SCD-related hospital visit compared to non-users (OR: 2.09; CI: 1.28 – 3.43). A

significant relationship was found between HU use and not only having a hospital visit, but also length ofstay in the hospital. HU users had a significantly higher average LOS (β: 0.49; CI: 0.14 – 0.84) compared to non-users. The relationship between HU use and having an SCD-related ED visit was not found to be significant (OR: 1.54; CI: 0.89 – 2.69). The results for the multivariable model assessing the relationship between HU use and costs are presented in Appendix B, Table 9. A Gaussian distribution was deemed appropriate for analyzing costs through the Modified Park's Test. The relationship between HU use and medical costs was not significant (β: 2,228; p=0.54).

DISCUSSION

This study assessed the impact of HU use on SCD-specific hospitalizations, ED visits, length of stay, and medical costs in children with SCD enrolled in Medicaid in 40 US states. This is the first study to evaluate the role of HU in health resource utilization among pediatric patients with SCD using a national longitudinal patient-level database. This study compared resource utilization and cost outcomes in a matched sample of HU users and non-users, thereby providing more robust results compared to previous studies.

HU users had a higher likelihood of having a hospitalization in the follow-up period compared to non-users. Although previous studies conducted in adults indicate otherwise, observational studies conducted in children have found similar results stating that HU use is associated with increase in resource use. A study by Lanzkron et al. found that in Maryland, hospitalizations among patients with SCD have increased since the approval of HU (1.006 hospitalizations per person in 1995 to 1.288 hospitalizations per person in 2003).[26] A previous study by Tripathi et al. reported that the HU-treated group of pediatric patients was more severely ill than the matched control group from the same SCD population.[27] Despite close matching on race, sex, age, years in data set, and baseline severity, the HU-treated group in this study had substantially more complications than the non-HU-treated group. Apart from splenic complications, almost all organ-specific complications were at least twice as high in the HU-treated group compared to the control group. Although we controlled for disease severity in the multivariable model, a proxy measure (patients who had three or more crises per year, or three or more episodes of ACS per year, or any combination of these amounting to three or more

episodes per year were categorized as having severe disease) was used for severity, which may not be able to completely control for confounding. Another study by Lanzkron et al. conducted in a managed care organization in Maryland found similar results.[28] Inpatient admissions for non-users were significantly lower than those for HU users (1.5 vs. 5; p = 0.004). HU users had an admission rate 3.9 times higher than non-users after controlling for sex, age, and outpatient visits. Also, infrequent HU users reported greater number of admissions compared to regular HU users. This study provides evidence to further support the hypothesis that HU users and non-users may differ greatly in terms of SCD severity. Using a better measure of disease severity that makes HU users and non-users more comparable is recommended for the future.

The relationship between HU use and having an ED visit was not found to be significant. A similar relationship was also reported in the study by Candrilli et al. using North Carolina Medicaid claims of pediatric patients.[20] Previous clinical trials demonstrating the benefit of HU use in preventing SCD-related adverse outcomes in children have been small studies with very few participants.[6,17,18] A controlled setting and smaller sample size in controlled trials limit the extrapolation of results at a population level. The failure of our study to corroborate the benefit of HU found in these trials raises questions regarding the effectiveness and safety of HU use in children.

HU users were found to have a longer length of stay compared to non-users. The Lanzkron et al. study described previously reported a mean LOS of 6.16 days in 1995 decreasing to 5 days in 2003.[26] The mean length of stay reported in our study (12.07 days) was higher than that reported in this study. Our study was conducted using Medicaid data from 40 states. Children enrolled in Medicaid are known to have greater number of hospitalizations (and re-hospitalizations) compared to those enrolled in other insurance types.[12,29] Since our length of

stay measure is cumulative (addition of all hospitalizations in the follow-up period), it is not surprising that the mean LOS reported in our study was higher than previously reported in children. Also, the follow-up period in which LOS was calculated in our study was more than a year given that HU users were identified in 2007 and LOS was calculated from the start of HU use to the end of 2008. This may be another reason why the LOS reported in our study was greater than Lanzkron study. Ballas et al. analyzed data from patient diaries, follow-up visit forms, and medical contact forms on the 299 patients enrolled in the Multicenter Study of Hydroxyurea and found no significant difference in the inpatient LOS between the HU group and placebo ($p = 0.74$).[30]

Medical costs incurred by HU users were not found to be significantly related to HU use after controlling for covariates. Several previous studies have reported higher costs for HU users in the pediatric population. The study conducted among pediatric patients enrolled in South Carolina Medicaid reported that total medical costs (emergency, outpatient, and inpatient costs) were significantly higher for HU users compared to non-users (RR: 2.10; CI: 1.64 – 2.71).[31] Emergency/inpatient costs among hydroxyurea users were significantly higher than non-users (RR: 2.11; CI: 1.65 – 2.69). In the study by Lanzkron et al., medical costs per month for HU users were significantly higher compared to non-users ($p<0.05$).[28] The authors suggested that the high costs associated with users of HU were due to the greater severity of their illness (compared to non-users) combined with low medication adherence to HU.

By providing evidence to suggest that HU use is associated with increased likelihood of hospitalization and a longer length of stay, our study questions the safety of HU use in the pediatric population. Short term adverse events associated with HU use include leukopenia, thrombocytopenia, and anemia.[32] Further investigation is required to indicate whether greater

resource use and costs associated with HU use are a result of side-effects of this medication. Our results along with those from previous observational studies indicate that although clinical trials have established the beneficial effect of HU in decreasing resource utilization events related to SCD among pediatric patients, population-based studies have reported otherwise. This disparity in research findings may be stemming from the fact that physicians tend to prescribe HU to patients with frequent painful crises, chronic pain with frequent narcotic use, and acute chest syndrome.[33] Regular use of HU is crucial for decreasing clinical outcomes and resource utilization. The aforementioned study by Lanzkron et al. noted that patients who had regular refills of HU had significantly fewer inpatient visits and lower costs compared to irregular users.[28] Unfortunately, the rates of adherence to HU in the pediatric population are very low. A study using the North Carolina Medicaid claims by Candrilli et al. reported that only 40% of the pediatric patients were adherent to HU therapy.[20] In addition, a sizable proportion of patients prescribed HU may be non-responders (25%).[34] HU being prescribed to children with more severe form of the disease, lack of adherence to HU in this population, and the high proportion of non-response to therapy may be collectively responsible for significantly greater resource utilization among HU users.

Another potential reason why our results differ from those obtained in previous studies conducted in the pediatric population is that these studies measured outcomes after a period of continuous HU therapy.[17–19] The study by Scott et al. found a significant reduction in hospitalizations from the pre-HU period to the post-HU period only among 10 patients completing one year of HU therapy.[19] Overall, the decrease was not found to be significant ($p=0.09$). This provides evidence to suggest that HU is useful in decreasing resource utilization; however, this benefit is only realized through continuous use of HU for a long period of time.

Due to limited data availability, we could not adopt a similar study design to test the long-term impact of HU use on resource utilization outcomes.

Our study has several strengths. First, ours is the first study that examines the relationship between HU use and short-term resource utilization and health care cost among pediatric patients with SCD. Although HU is not approved for use in pediatric patients with SCD, physicians prescribe HU in this population in cases where the disease is severe. The results of this study can serve to inform prescribers that short-term beneficial effects of HU may not be realized if regular use of HU is not ensured. Second, since our study uses observational data in the form of Medicaid claims, it provides real-world population estimates for the impact of HU use on resource utilization and cost outcomes in pediatric patients with SCD. Third, ours is the first study conducted using Medicaid data from 40 states in the US, which has an advantage in terms of external validity over previous observational studies, conducted within a single state. The results from this study can be generalized to the pediatric Medicaid population with SCD.

This study also has some limitations that are worth mentioning. First, we identified patients who had 3 fills of HU in a period of 6 months as HU users. However, there is no way to be certain that these patients continued taking the medication after this time. Furthermore, research suggests that up to 25% of patients might be non-responders to HU.[34] Since this is an observational study, there is no way for us to ensure that all patients classified as HU users were responders. Continued use of HU and response to HU can affect resource utilization, both of which were not accounted for in our study. Second, we used a period of one year (calendar year 2006) to establish HU naivity in the cohort of SCD patients. However, we cannot be certain that the sub-cohort of HU naïve patients thus obtained is truly HU naïve, as they may have had HU

prescriptions before 2006. However, even if such a scenario persists, it is unlikely that any HU use before 2006 will affect outcomes in 2008.

Previous clinical trials have shown the beneficial effect of HU in decreasing SCD-related complications among pediatric patients. Our study aimed at testing whether the potential beneficial effect of HU translates into decreased resource utilization and healthcare costs in this population. However, we did not find evidence to support that HU use decreases short-term resource utilization and costs among pediatric Medicaid enrollees with SCD. In fact, our study reported a greater risk of having an inpatient visit and longer length of stay among HU users. Future studies should aim at understanding the reasons for increased resource utilization among users of HU. Healthcare providers caring for pediatric patients with SCD should weigh the benefits and risks associated with HU use before prescribing it in this population. Most clinical trials have reported the beneficial effects of HU use on resource utilization in children more than one or two years after the initiation of HU therapy. Future observational studies should aim at assessing the impact of HU use on long-term resource utilization in pediatric patients. Observational research may be subject to unobserved confounding due to vast differences in the two treatment groups. Future studies should attempt to control for unobserved confounding when testing the relationship between HU use and economic outcomes. If evidence for beneficial effects of HU in the pediatric population with SCD is seen at the population level, it has the potential for becoming a front-line treatment for children suffering from this debilitating disease.

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LIST OF APPENDICES

APPENDIX A – IDENTIFICATION CODES

Table 1: ICD-9-CM codes for sickle cell disease

ICD-9-CM* code	Description
282.41	Sickle-cell thalassemia without crisis
282.42	Sickle-cell thalassemia with crisis
282.6	Sickle-cell disease
282.60	Sickle-cell disease, unspecified
282.61	Hb-SS disease without crisis
282.62	Hb-SS disease with crisis
282.63	Sickle-cell/Hb-C disease without crisis
282.64	Sickle-cell/Hb-C disease with crisis
282.68	Other sickle-cell disease without crisis
282.69	Other sickle-cell disease with crisis

*ICD-9-CM: International Classification of Diseases, 9th Revision, Clinical Modification

Table 2: NDC codes for hydroxyurea

NDC code	Trade name	Strength
0003-0830	Hydrea capsules	500 mg/1
0003-6335	Droxia capsules	200 mg/1
0003-6336	Droxia capsules	300 mg/1
0003-6337	Droxia capsules	400 mg/1
68084-284	Hydroxyurea capsules	500 mg/1
0555-0882	Hydroxyurea capsules	500 mg/1
49884-724	Hydroxyurea capsules	500 mg/1
54868-4773	Hydroxyurea capsules	500 mg/1
54868-4773	Hydroxyurea capsules	500 mg/1
54868-4773	Hydroxyurea capsules	500 mg/1
54868-4773	Hydroxyurea capsules	500 mg/1
54868-4773	Hydroxyurea capsules	500 mg/1
60429-265	Hydroxyurea capsules	500 mg/1

NDC = National drug classification; mg/l =milligrams per liter.

Table 3: CPT-4, HCPCS procedure, and revenue codes for blood transfusion

Code type	Code	Description
CPT-4	36450	Exchange transfusion, blood; new born
CPT-4	36455	Exchange transfusion, blood; other than new born
CPT-4	36520	Erythrocytapheresis
CPT-4	36521	Erythrocytapheresis
CPT-4	36512	Therapeutic apheresis for red blood cells
HCPCS	P9010	Blood (whole), for transfusion, per unit
HCPCS	P9016	Red blood cells, leukocytes reduced, each unit
HCPCS	P9021	Red blood cells, each unit
HCPCS	P9022	Red blood cells, washed, each unit
HCPCS	P9038	Red blood cells, irradiated, each unit
HCPCS	P9039	Red blood cells, deglycerolized, each unit
HCPCS	P9040	Red blood cells, leukocytes reduced, irradiated, each unit
HCPCS	C1010	Whole blood or red blood cells, leukocytes reduced, CMV-negative, each unit
HCPCS	C1016	Whole blood or red blood cells, leukocytes reduced, frozen, deglycerol, washed, each unit
HCPCS	C1018	Whole blood, leukocytes reduced, irradiated, each unit
Revenue	380	Blood
Revenue	381	Packed red cells
Revenue	382	Whole blood
Revenue	389	Other blood
Revenue	390	Blood storage
Revenue	391	Blood administration
Revenue	399	Other blood storage and processing

CPT-4 = Current procedural terminology 4th edition;
HCPCS = Healthcare common procedure coding system.

APPENDIX B – RELATIONSHIP BETWEEN HU USE AND ECONOMIC OUTCOMES

Table 4: Characteristics of the matched sample

Variable	HU users (N=238)	HU non-users (N=238)	p value
Race			0.0008
Black	132 (55.46)	161 (67.65)	
Non-black	106 (44.54)	77 (32.35)	
Blood transfusion			<0.0001
Yes	96 (40.34)	50 (21.01)	
No	142 (59.66)	188 (78.99)	
Comprehensive sickle cell center			<0.0001
Yes	78 (32.77)	75 (31.51)	
No	160 (67.23)	163 (68.49)	
Opioid use			<0.0001
Yes	174 (73.11)	123 (51.68)	
No	64 (26.89)	115 (48.32)	
Disease Severity			<0.0001
Yes	129 (54.20)	53 (22.27)	
No	109 (45.80)	185 (77.73)	
No. of blood transfusions	1.60 (3.27)	1.28 (4.01)	0.3606
No. of office visits, Mean (SD)	14.20 (11.30)	12.24 (16.94)	0.1739
No. of opioid prescriptions	2.69 (3.03)	1.26 (2.01)	<0.0001

HU = Hydroxyurea; SD = Standard Deviation

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Table 5: Univariable analyses demonstrating relationships between hydroxyurea use and outcomes in the matched sample

Variable	HU user (N = 238)	HU non-users (N = 238)	P value
Hospitalization, N (%)			0.0035
Yes	164 (68.91)	114 (47.90)	
No	74 (31.09)	124 (52.10)	
ED visit, N (%)			<0.0001
Yes	182 (76.47)	143 (60.08)	
No	56 (23.53)	95 (39.92)	
Length of stay, Mean (SD)	17.78 (23.95)	6.36 (16.10)	<0.0001
Medical Costs, Mean (SD)	31,847.16 (36,516.36)	19,237.07 (44,820.67)	<0.0001

HU = Hydroxyurea; SD = Standard Deviation

Table 6: Conditional logistic regression analysis assessing the relationship between hydroxyurea use and having a hospitalization event

Independent variable	Odds Ratio	Confidence Interval
Hydroxyurea use		
Yes	2.09	1.28 - 3.43
No		
Race		
Black	0.82	0.38 - 1.80
Non-Black		
Previous blood transfusion		
Yes	1.90	0.84 - 4.32
No		
Comprehensive center in the state of residence		
Yes	1.24	0.60 - 2.57
No		
Previous opioid prescription		
Yes	0.74	0.35 - 1.56
No		
Disease severity		
Yes	2.05	1.01 - 4.17
No		
Number of office visits	1.01	0.99 - 1.03

Table 7: Conditional logistic regression analysis evaluating the relationship between hydroxyurea use and having an emergency department visit

Independent variable	Odds Ratio	Confidence Interval
Hydroxyurea use		
Yes	1.54	0.89 - 2.69
No		
Race		
Black	1.30	0.59 - 2.86
Non-Black		
Previous blood transfusion		
Yes	2.69	0.99 - 7.27
No		
Comprehensive center in the state of residence		
Yes	1.56	0.72 - 3.38
No		
Previous opioid prescription		
Yes	1.02	0.45 - 2.31
No		
Disease severity		
Yes	3.04	1.43 - 6.48
No		
Number of office visits	0.99	1.00 - 1.03

Table 8: Poisson regression assessing the relationship between hydroxyurea use and length of stay

Independent variable	Parameter Estimate	Confidence Interval
Hydroxyurea use		
Yes	0.49	0.14 - 0.84
No		
Race		
Black	-0.24	-0.55 - 0.08
Non-Black		
Previous blood transfusion		
Yes	0.51	0.24 - 0.78
No		
Comprehensive center in the state of residence		
Yes	0.36	0.03 - 0.58
No		
Previous opioid prescription		
Yes	0.10	-0.05 - 0.77
No		
Disease severity		
Yes	1.00	0.67 - 1.33
No		
Number of office visits	0.01	-0.01 - 0.01

Table 9: Generalized linear model predicting the effect of hydroxyurea use on costs

Independent variable	Parameter Estimate	p value
Hydroxyurea use		
Yes	2,228.12	0.54
No		
Race		
Black	-4978.64	0.16
Non-Black		
Previous blood transfusion		
Yes	22,114.29	<0.01
No		
Comprehensive center in the state of residence		
Yes	9,849.34	<0.01
No		
Previous opioid prescription		
Yes	236.25	0.95
No		
Disease severity		
Yes	13,927.47	<0.01
No		
Number of office visits	473.27	<0.01

CHAPTER 5

DISCUSSION

The goal of this chapter is to conclude this dissertation with a general discussion. First, key findings will be summarized, followed by implications of this research. This chapter will conclude with overall strengths and limitations of this dissertation, directions for future research and a brief conclusion.

Summary of key findings

This dissertation sought to report the prevalence and predictors of use of hydroxyurea (HU), and its impact on clinical outcomes, resource utilization, and costs in pediatric Medicaid beneficiaries with sickle cell disease (SCD) enrolled in 40 US states. The prevalence of HU use in this population was found to be 10.72%. Predictors of HU use spanned from demographic variables, including age, gender, and race to health-related predictors, including disease severity, prior opioid prescriptions, previous office visits, and presence of a comprehensive sickle cell center within the state of residence. Although HU use did not have a significant impact on likelihood of having a sickle cell crisis, HU users were found have a significantly higher number of crises compared to non-users after controlling for the effects of observed covariates in a conventional multivariable model. After controlling for the effects of unobserved confounding through the use of instrumental variables (IVs), the relationship between HU use and number of sickle cell crises became negative, but was statistically insignificant. Lastly, HU users had a significantly higher likelihood of having a hospitalization compared to non-users. The length of stay was also found to be significantly longer among HU users.

Implications of the study

The results reported in this dissertation have implications for researchers and healthcare providers treating children with SCD. This study reported that the utilization of HU in the pediatric Medicaid population with SCD is only 10.72%. Given that HU is not approved by the US Food and Drug Administration (FDA) for use in the pediatric population, and there is uncertainty regarding its safety and effectiveness in treating SCD-related complications in this population, our study provides evidence to suggest that providers are exercising caution when prescribing this drug in this population. Also, the finding that health-related predictors that are indicators of severe disease (SCD severity, prior office visits, and prior opioid use) positively predicted the prescription of HU supports the fact that physicians treating these patients with SCD follow guidelines that have been put in place for effective use of HU in this population.[1] Unlike previous clinical trials, this study did not find evidence to support that HU use decreases clinical complications and resource utilization in the pediatric SCD population.[2–9] This finding calls for caution among health-care providers using HU to treat SCD-related complications in children. This dissertation points to the fact that although clinical trials are required for drug approval and labeling purposes, they are conducted in a controlled setting, and the results obtained in these trials may not be supported by population-based studies. The decision to prescribe a particular drug in a segment of the population in which it is not approved should be based on treatment guidelines and research conducted in the form of clinical trials as well as population-based studies.

Our study found a difference in the results obtained through conventional multivariable regression controlling for observed confounders and IV analysis that can control for observed as well as unobserved confounding when assessing the relationship between HU use and number of

sickle cell crises. Unobserved confounding exists when the two groups being compared (HU users and non-users) are inherently different. Not only should results of previous observational studies assessing the impact of HU use on clinical outcomes and resource utilization be interpreted with caution, researchers conducting such studies in the future should account for unobserved confounding so as to make the results more robust and valid.

Strengths and limitations of the study

This is the first study to report the prevalence and predictors of HU in pediatric patients with SCD using nationwide Medicaid claims data from 40 US states. Since HU is not approved by the US FDA for use in this population, it is important to ensure that this drug is being utilized appropriately. Ours is the first study to shed some light on characteristics that determine the prescription of HU in pediatric patients with SCD, and may assist in the decision-making process for prescribers treating such patients.

Using insurance claims data for evaluating outcomes associated with medication use has several advantages over clinical trials conducted to test drug efficacy. Claims data represent real-world medication use, and are thus capable of providing real-world population-based estimates as opposed to clinical trials in which medication use is controlled in a small sample of participating patients. This dissertation, which used Medicaid claims data from 40 US states has a definite advantage in its generalizability.

This is the first large-scale observational study with a view to assess the prevalence and predictors of HU use and its impact on clinical and resource utilization outcomes in the pediatric population with SCD conducted using Medicaid claims data from 40 US states. SCD is mainly prevalent in the African-American and Hispanic population, representing almost 50% of

beneficiaries enrolled in Medicaid programs nationwide.[10] Also, pediatric beneficiaries contribute to a high 58% of the national Medicaid population.[11] Previous research has documented that the majority of SCD patients seeking healthcare are covered by government insurance.[12,13] Given the lower than average life-span of those suffering from the disease, it is reasonable to assume that most of the pediatric patients with SCD are covered by Medicaid. Thus, our study has the advantage of being more generalizable to the SCD population in the US compared to the retrospective observational studies conducted previously with a similar goal.[14–16]

This study uses robust methods of analyses to compare sickle cell crises, resource utilization, and costs among HU users and non-users. All analyses comparing the presence or absence of outcomes included a sample of HU users and non-users matched on age and gender. An additional outcome, number of sickle cell crises, was compared between HU users and non-users using a conventional multivariable model controlling for the effect of observed confounding as well as an IV approach additionally controlling for the effect of unobserved confounding. Standard regression techniques can only control for observed differences between the patients who receive treatment, and those who do not by adding them as covariates in the regression model. However, they do not control for confounding that is unobservable to the researcher, which stems from selection bias prevalent in observational research because of patients in the two treatment groups being inherently different from one another. This study has a clear methodological advantage over other observational studies conducted using conventional multivariable approaches only.

Medical and prescription claims data may suffer from coding errors during claims processing. For example, the primary and secondary ICD-9-CM code for a patient visiting a physician's office for a sickle cell crisis may be incorrectly coded as the ICD-9-CM code for

sickle cell disease. Since we used ICD-9-CM codes to identify outcomes in this study, there is a possibility that some outcomes may be incorrectly identified. However, an assumption can be made that these errors are distributed evenly in both, the treatment and untreated groups, thus nullifying their effect on the outcomes.

Another disadvantage of using secondary claims data is that proxies have to be used when measuring certain parameters. For example, we used at least three prescription fills in a period of six months as a measure of HU use. However, there is no way of knowing whether HU users continued taking HU after those three fills, for how long they took HU while in the study period, what were the reasons for discontinuation of HU, etc. There was also no way of knowing whether patients identified as HU users were on an HU prescription during the time of measurement of the outcome.

Directions for future research

This study evaluated demographic and health-related predictors for HU use in children with SCD. Since HU is not approved by the US FDA for use in SCD children, there may be some physician-related factors such as specialty, practice patterns, location, etc. that may influence the use of HU in this population. Future studies should explore these physician-related predictors to gain more insight into the utilization patterns of HU in this population.

Our study was unable to corroborate the beneficial effect of HU on clinical outcomes in children with SCD that was apparent in previous clinical trials. We tried to control for unobserved confounding by the use of IVs, but there may still be some amount of unobserved confounding that our study did not account for. Future researchers should explore the use of

novel IVs or use other methods while testing relationships between HU use and clinical outcomes and resource utilization in the pediatric population with SCD.

In conclusion, this study is the first of its kind to report the prevalence and predictors of HU treatment in children with SCD enrolled in the Medicaid programs in 40 US states. The prevalence of HU use in this population was found to be low, and was associated with certain demographic and health-related factors. Our study was unable to establish the beneficial effect of HU on clinical outcomes and resource utilization, thus warranting the need for more observational real-world studies with robust methodologies in this population.

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VITA

Summary

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Research Analyst, Center for Pharmaceutical Marketing and Management (CPMM), University of Mississippi (June 2011 to February 2014).

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Teaching Assistant, University of Mississippi (August 2010 to December 2010).

Teaching Assistant, St John's University (May 2009 to June 2010).

Research Intern, Ar-Ex Pharmaceuticals (June 1, 2007 to July 31, 2007).

Publications

Datar M, Khanna R. Inpatient burden of gastro-intestinal stromal tumors (GISTs) in the United States. Journal of Gastrointestinal Oncology. 2012; 3(4): 335–341.

Datar M, Yang Y, Mahabaleshwarkar R, Bentley JP, Banahan BF III. Comparative effectiveness of on-pump versus off-pump coronary artery bypass grafting among elderly patients - a propensity score-matched analysis. Health Outcomes Research in Medicine. 2012; 3: e221-e230.

Datar M, Holmes E, Adams A, Stolpe S. Pharmacy students' perceptions of community pharmacy residency programs. Journal of American Pharmacists Association. 2013; 53:2.

Mahabaleshwarkar R, Yang Yi, Datar M, Bentley JP, Null KD, Strum M. Risk of adverse cardiovascular outcomes and all-cause mortality associated with concomitant use of clopidogrel and proton-pump inhibitors in elderly patients. Current Medical Research and Opinion. 2013; 29 (4): 315-323.

Khanna R, Pace PF, Mahabaleshwarkar R, Basak RS, Datar M, and Banahan BF III. Medication Adherence for Chronic Diseases among Recipients Enrolled in a State Medicaid Program. Population Health Management. 2012; 15(5): 253-60.

Athavale A, Datar M. 2011-2012 ISPOR Student Survey. ISPOR Connections. 2012; 18 (4): 13.

Datar M, Shahpurwala Z. 2012-2013 ISPOR Student Survey. ISPOR Connections. 2013; 19 (4).

Podium presentations

Datar M, Yang Y, Mahabaleshwarkar R, Bentley JP, Banahan BF III. Comparative effectiveness of on-pump and off-pump coronary artery bypass grafting among elderly patients – A retrospective analysis of Medicare claims data. Presented at the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Annual International Meeting. June 2012, Washington DC.

Datar M, Yang Y, Bentley JP, Banahan BF III, Mahabaleshwarkar R. Economic outcomes associated with on-pump versus off-pump coronary artery bypass grafting (CABG) in high risk elderly patients. Presented at Meeting in the middle. June 2012, Austin, TX.

Mahabaleshwarkar R, Yang Y, Datar M, Bentley JP, Strum M, Banahan BF III, Null KD. Risk of adverse cardiovascular outcomes and all-cause mortality associated with concomitant use of

clopidogrel and proton-pump inhibitors in elderly patients. Presented at the ISPOR Annual International Meeting. June 2012, Washington DC.

Jariwala K, Data M, West-Strum D, Banahan BF III, Ross LA, Bloodworth LS. Demographic variation and patient reported outcomes at enrollment in a medication therapy management (MTM) program in the Mississippi Delta. Presented at the Consortium for Health Education, Economic Empowerment and Research Conference. July 2011, Memphis, TN.

Awards and Honors

Graduate achievement award in Pharmacy Administration, Honors Convocation, University of Mississippi

Research paper of the year award (Mahabaleshwarkar R, Yang Yi, Datar M, Bentley JP, Null KD, Strum M. Risk of adverse cardiovascular outcomes and all-cause mortality associated with concomitant use of clopidogrel and proton-pump inhibitors in elderly patients Current Medical Research and Opinion. 2013; 29 (4): 315-323).

ISPOR Student Network Distinguished Service Award, May 2013.

Best podium presentation (Datar M, Yang Y, Mahabaleshwarkar R, Bentley JP, Banahan BF III. Economic outcomes associated with on-pump versus off-pump coronary artery bypass grafting (CABG) in high risk elderly patients), Meeting in the middle. June 2012, Austin, TX.

APhA-APPM best poster presentation (Datar M, Holmes E, Adams A, Stolpe S. Pharmacy students' perceptions of community pharmacy residency programs), APhA Annual Meeting. March 2012, New Orleans, LA.

Poster finalist (Mahabaleshwarkar R, Yang Y, Datar M, Bentley J, Null KD, Strum M, Banahan BF III. Risk of adverse cardiovascular outcomes and all-cause mortality associated with concomitant use of clopidogrel and proton-pump inhibitors in elderly patients) ISPOR Annual International Meeting. June 2012, Washington DC.

Member of Phi Kappa Phi (March 2015 to present)

Member of Chi Chapter, Rho Chi - An Academic Honors Society in Pharmacy (February 2012 to present)

Scholarship to attend the Pharma SAS users group (PharmaSUG) meeting. May 2011, Nashville, TN.

Scholarship to attend the Drug Information Association's 47th Annual Meeting. June 2011, Chicago, IL.