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Hydroxyurea in Children with Sickle Cell Disease: Practice Patterns and Barriers to Utilization

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Abstract

Hydroxyurea (HU) is underutilized in adults with sickle cell disease (SCD) despite the Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH) (1). Since little is known about HU utilization in children with SCD we sought to: 1) evaluate patterns of HU utilization; 2) elicit how providers define frequent pain when prescribing HU; and 3) identify barriers to HU use by surveying members of the American Society of Pediatric Hematology/Oncology. Data analysis included descriptive statistics and Chi-square. Of the 350 respondents, 63% care for SCD patients. Of these providers, only 9% have 50–90% of patients on HU, while 10% have <10% on HU. Criteria used to initiate HU included acute chest syndrome and frequent pain. Approximately half of providers account only for pain requiring hospitalization when prescribing HU. Those accounting for pain managed at home were more likely to have >30% of patients on HU (35.2% vs. 20%; p=0.023; Chi-square). Provider-related barriers to prescribing HU included compliance with: HU (86%), laboratory monitoring (85%), and contraception (85%). Our survey suggests substantial variation in HU utilization in children. Providers accounting for pain managed both in and out of the hospital had more patients on HU. Existing barriers to HU utilization should be addressed to optimize care for children with SCD.

Keywords

hydroxyurea; sickle cell disease; children; utilization; barriers

Pain is the most common complication of SCD accounting for over 80% of all hospitalizations for children. Home pain diary studies reveal pain is also frequently managed at home and goes underreported (2–4). Treatment of painful events primarily involves symptomatic care. Preventative measures are limited and HU, an oral drug taken once daily, is the only drug shown to decrease the frequency of SCD painful events (1).

The efficacy of HU was proven in adults in 1995 through a randomized controlled trial, the MSH (1). The MSH found HU significantly reduced the annual rate of painful events, acute chest syndrome episodes, and transfusions (1). The 9 year follow-up to MSH revealed HU was associated with significant reduction in mortality, minimal side effects, and was safe (5). A large trial mimicking the MSH in children was not conducted. However, efficacy

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studies in children include a randomized, placebo controlled, cross-over trial with small numbers of children and open-label, single-arm studies (6–8). These studies demonstrated a significant decrease in painful events in the HU arm (6–8) and led to the introduction of HU into pediatric practice for the prevention of pain. Subsequent studies have proven safety and hematologic efficacy in children (9–12).

Since the efficacy of HU was established in a controlled clinical trial environment, its effectiveness is dependent upon its utilization in real clinical practice. Despite the impressive findings of the MSH, HU is underutilized in adults limiting its effectiveness (13,14). The National Institutes of Health (NIH) Consensus Development Conference Statement confirmed this underutilization (15). The utilization of HU in children has never been studied, thus no data exist to support whether its utilization will be better in pediatrics.

The NIH published recommendations for HU in children and adults in 2002 stating HU should be initiated in patients with “frequent pain episodes” (16). Currently, there are no national data addressing how pediatric SCD providers define “frequent pain episodes” and how they use this definition to recommend HU. Emerging SCD pain literature reveals majority of pain episodes are managed at home (2–4,17) and it is unknown if providers incorporate these data into their definition of frequent pain.

To assess these important knowledge gaps we surveyed pediatric hematology/oncology providers and sought to achieve the following objectives: 1) evaluate practice patterns of HU utilization in children with SCD; 2) elicit how providers define frequent pain when prescribing HU; and 3) identify barriers to HU use.

Overall there was a 31% response rate (n=350). Of those that responded, 63% (n=220) take care of SCD patients. The majority of SCD providers were physicians (n=213; 96.8%), about half were female (n=103; 46.8%). The median years in practice was 12 (IQR 5–20). See online supplement for additional provider demographics and characteristics of practice and flow diagram of final study population (Table I, Figure 1).

Most providers (90%) felt HU was effective or very effective for the prevention of pain. Only 9% of providers have 50–90% of their patients on HU, 22% have 31–50% on HU, 54% have 10–30% on HU, and 10% have <10% on HU. Table II shows the most common criteria providers use to start HU. About half (54%) indicated they initiated HU in children <4 years of age.

Figure 2 displays how providers define frequent pain in children with SCD. When asked about criteria used to initiate HU for pain, 42% used only pain requiring hospitalization whereas 44% accounted for pain both at home and in the hospital when prescribing HU. Importantly, providers incorporating pain at home into their definition of frequent pain were more likely to have >30% of their patients on HU (35.2% vs. 20%; p=0.023; Pearson Chi-square).

The proportions of providers stating a particular factor influenced their decision to *not* prescribe HU to eligible patients are listed in Table III. The most common factors identified as barriers to prescribing HU revolved around the theme of compliance.

Twenty-six percent of providers reported >20% of their patients/families refused HU when it was offered. The most common reasons for patients’ refusal were fear of cancer (51%) and other side effects (62%), don’t want to take medication (49%), or don’t want required laboratory monitoring (28%). Interestingly, 17% refused HU because they didn’t think it would work.

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To our knowledge, this is the first study to assess utilization of HU in children with SCD and to identify barriers to its use in children. Our survey suggests substantial variation exists in the use of HU in children with SCD. Very few providers have more than half of their patients on HU and 1 in 10 rarely use HU and have <10% of patients on HU.

Our survey also found providers use HU for SCD-related complications without data to support its use for these complications, representing clinical drift (18). Over a third of providers use HU for secondary stroke prevention and almost half use HU for priapism and pulmonary hypertension; all complications currently lacking HU efficacy data. These data raise the need for continued and future funding of clinical trials to evaluate the unknown efficacy of HU for these complications which will prevent or promote the appropriate use of HU and ultimately avoid clinical drift (18).

Fortunately, majority of providers use frequent pain as criteria for starting HU, however, how providers define frequent pain varied. Our data show almost half of providers use only pain events requiring hospitalization as criteria for starting HU. If this strict definition is used, many children that may benefit from HU will not be considered eligible. Recent pain literature in SCD reveals majority of pain is managed at home (2–4,17), goes underreported and impacts school attendance and children's health-related quality of life (2–4,19,20). Our survey found providers accounting for pain at home were significantly more likely to have more children on HU, suggesting how providers define frequent pain may be a barrier to using the drug.

The identified barriers to HU use in children at the provider and patient level were similar to previously identified barriers in adults with SCD (13,14,21). The most common provider-related barriers involved the theme of patient compliance, including compliance with taking HU, required laboratory monitoring, and female contraception. Importantly, non-compliance may be a result of poor access to care, a systems-level barrier, or may stem from patients' fears of side effects. In addition, patients' access to HU may be limited if providers are not prescribing HU to eligible patients because of their own biases about the drug.

Other barriers included concerns for toxicities there may or may not be evidence to support, such as concern for carcinogenesis. Long-term follow-up data from MSH do not provide evidence supporting this concern in adults taking HU (5). The Agency for Healthcare Research and Quality systematic review about HU also stated "limited evidence suggests that HU treatment in adults with SCD does not increase the risk for leukemia" (22). Widespread provider and patient education regarding the limited or non-existent association between HU and cancer is imperative to eliminate this barrier. Concern for male infertility was a provider-related barrier in almost half. Currently, evidence is lacking to support or disprove this concern. Concern for teratogenesis was a fear for majority of providers and if the provider doubted compliance with female contraception, this was a barrier to the use of HU. Current MSH data reveal harm did not occur to offspring of women taking HU at the time pregnancy occurred (23). Finally, although some providers place children <4 years on HU, majority of providers reported age (patient too young) was a barrier to prescribing HU. Data from the trial "HU to Prevent Organ Damage in Children with Sickle Cell Anemia" (24) will confirm the safety of HU in young children and potentially reduce the barrier of age in the prescribing of HU to younger children that may benefit.

Ultimately, it is important to remember SCD carries with it significant morbidity and is associated with mortality. Based on proven efficacy and safety in children (6–12,25,26) , HU provides significant benefit to children suffering from a life-long debilitating disease and likely improves their health-related quality of life; thus the benefit of HU may outweigh potential risks.

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Our study is limited in that survey responses may not reflect true practice. Individual charts would require auditing to verify this information. In addition, we do not have information about non-responders since the survey was anonymous. The overall response rate was 31%, however this is consistent with other published survey research (27–29).

In conclusion, our survey suggests substantial variation in HU utilization in children with SCD. HU is used for complications other than pain despite insufficient evidence for its efficacy for these complications, representing clinical drift (18). Studies to determine the efficacy of HU for SCD complications other than pain are urgently needed to prevent or promote the appropriate use of the drug. Although majority of providers report frequent pain as criteria for starting HU, almost half only account for pain bringing a child to the hospital. This strict definition likely misses many children experiencing significant pain at home that would benefit from HU. Finally, provider, patient, and systems-level barriers to HU utilization in children exist and need to be addressed. Future studies should be aimed at evaluating unknown toxicities of HU that influence practice, exploring whether access to care contributes to noncompliance, adherence research, and provider education about the extent of pain experienced by children with SCD.

Methods

An anonymous cross-sectional survey was emailed to 1316 pediatric hematology/oncology providers identified through the published 2008 American Society of Pediatric Hematology/Oncology (ASPHO) membership directory. ASPHO is an international professional society of pediatric hematology/oncology providers who conduct research in and treat children with cancer and other blood diseases. The survey was kept anonymous to encourage providers to be honest with their responses and the anonymity also permitted multiple respondents from the same institution to report their practice patterns as individuals allowing for variability of practice within a large program. This limited biasing responses of individuals towards the views and practices of the institution. The survey was adapted with permission from that done by adult SCD providers (13), pilot-tested amongst experts in pediatric SCD, modified based on their recommendations, and emailed using a web-based survey program (30). A brief introductory letter explained the study and stated informed consent was implied with survey completion. The initial email and five reminder emails were sent between February 12, 2009 and July 13, 2009 with reminder emails sent only to non-responders. The survey program allowed for completion of the survey only once by each member emailed. The survey began by identifying providers that care for SCD patients. If the provider did not care for SCD patients, the first question indicated this and the survey was complete. If the provider did care for SCD patients, he/she was directed to complete the remainder of the survey. The response rate includes all respondents, however, all other data includes only those that care for SCD patients. See online supplement for survey details addressing the main manuscript objectives. The study was approved by the Institutional Review Board of the Children's Hospital of Wisconsin, which allowed for completion of the survey to serve as implied consent.

Statistical Analysis

Analyses were conducted with SPSS version 14.0 for Windows (SPSS, Chicago, IL). Respondent survey data was extracted, inputted into SPSS, and descriptive statistics were calculated. We report proportions, medians and interquartile ranges as appropriate. Chi-square analysis was used to test differences between proportions. A p-value of ≤ 0.05 was considered statistically significant.

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Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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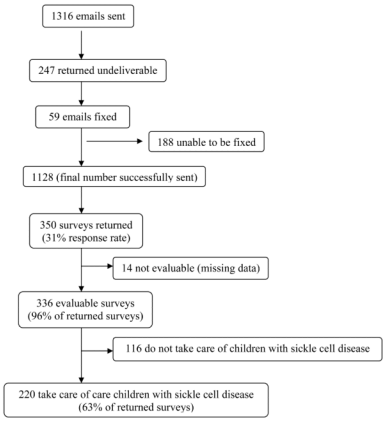

Figure 1.
Flow diagram of final study population.

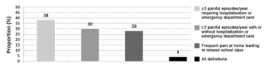

Figure 2.
Proportion of providers using various definitions for frequent pain in children with sickle cell disease.

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Table I

Provider Demographics and Characteristics of Practice (n=220)

Variable	N (%)
Race	
White, Non-Hispanic	161 (73.2)
Black	9 (4.1)
Hispanic	8 (3.6)
Asian or Pacific Islander	33 (15)
Native American	1 (0.5)
Other	8 (3.6)
Region of Practice (in US)	
Northeast	52 (23.6)
Midwest	45 (20.5)
South	70 (31.8)
West	36 (16.4)
Not in US	17 (7.7)
Patient Type (pediatric vs. adult)*	
Pediatrics	179 (84.4)
Adults	1(0.5)
Both Pediatrics and Adults	26 (12.3)
Practice Type	
Hematology	48 (21.8)
Oncology	1 (0.5)
Hematology/Oncology	170 (77.7)
Hospital Type*	
Rural teaching	8 (3.8)
Rural non-teaching	5 (2.4)
Urban teaching	178 (84)
Urban non-teaching	14 (6.6)

* some missing data; US= United States

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Table II

Criteria used by providers to start hydroxyurea

Criteria	Proportion (%)
Acute Chest Syndrome	88
≥3 painful episodes/year	86
Requiring hospitalization only	42
At home or requiring hospitalization	44
Chronic pain requiring frequent narcotic use	70
Priapism	48
Pulmonary Hypertension	43
Symptomatic Anemia	40
Stroke	36
Renal Failure	15
Ankle Ulcers	12
Low hemoglobin F levels	9
Elevated white cell count without evidence of infection	6

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Table III

Provider-related barriers to hydroxyurea use

Barrier	Proportion (%)
Patient compliance with taking medication	86
Patient compliance with blood tests	85
Lack of contraception in females	85
Patient's anticipation of side effects	75
Patient is too young	68
Concern for male infertility	46
Lack of formal guidelines for use in children	30
Provider discomfort with carcinogenic potential	27
Cost	18
Lack of time/resources to explain risks/benefits	16
Not FDA approved in children	12
Doubt effectiveness of hydroxyurea	11