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Hydroxyurea and acute painful crises in sickle cell anemia: Effects on hospital length of stay and opioid utilization during hospitalization, outpatient acute care contacts, and at home

Samir K. Ballas, MD, FACP
Thomas Jefferson University, samir.ballas@jefferson.edu

Robert L. Bauserman, PhD
Maryland Medical Research Institute

William F. McCarthy, PhD
Maryland Medical Research Institute

Oswaldo L. Castro, MD
Howard University

Wally R. Smith, MD
School of Medicine, Virginia Commonwealth University

See next page for additional authors

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Authors
Samir K. Ballas, MD, FACP; Robert L. Bauserman, PhD; William F. McCarthy, PhD; Oswaldo L. Castro, MD; Wally R. Smith, MD; and Myron A. Waclawiw, PhD

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Samir K. Ballas[1], Robert L. Bauserman[2], William F. McCarthy[2], Oswaldo L. Castro[3], Wally R. Smith[4], Myron A.Waclawiw[5] and the Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia

[1] Cardeza Foundation for Hematologic Research, Department of Medicine, Jefferson Medical College, Thomas Jefferson University, Philadelphia, PA USA, [2] Maryland Medical Resrarch Institute, Baltimore, MD USA, [3] Howard University, Wasfington, DC, USA, [4] Virginia Commonwealth University, Internal Medicine – Quality Health Care, Richmond, VA, USA, [5] National Heart, Lung and Blood Institute, Bethesda, Maryland, USA

Corresponding author: Samir K. Ballas MD, FACP, Cardeza Foundation, Department of Medicine, Jefferson Medical College, Thomas Jefferson University,1015 walnut Street, Philadelphia, PA 19107, Phone: 215-955-8485, Fax: 856-795- 0809, E-mail: samir.ballas@jefferson.edu

Emails: samir.ballas@jefferson.edu, rbauserman@mmri.org, wmccarthy@mmri.org, OLcastro@aol.com, wrsmith@hsc.vcu.edu, waclawim@nhlbi.nih.gov

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Abstract

Recurrent acute sickle cell painful crises are the hallmark of sickle cell anemia. These events may be mild, moderate or severe in nature and often require treatment at home, in acute care facilities as outpatients, and in the hospital with oral and/or parenteral opioids. The type, dose, route & frequency of administration of opioids, as well as the length of hospital stay (LOS), are not well known for adults with sickle cell anemia (SS). We analyzed these aspects in the 299 patients enrolled in the Multicenter Study of Hydroxyurea (MSH) in SS. For these patients there were 16818 home diaries, 2249 acute care contacts, and 2209 hospitalizations. At home analgesics were used on 40% of diary days and 80% of 2-week follow up periods, with oxycodone and codeine the most frequently used. Responders to hydroxyurea (HU) used analgesics on fewer days. During hospitalization 96% were treated with parenteral opioids, with meperidine the most frequently used; oxycodone was the most commonly used oral medication. The average LOS for responders to HU was about two days less than for other groups and their cumulative time hospitalized during the trial was significantly less than for nonresponders or placebo groups ($p<0.022$). They also had the lowest doses of parenteral opioids during acute care crises ($p=.015$).

Introduction

Sickle cell anemia (SS) is a quadrumvirate of pain syndromes, anemia and its sequelae, organ failure including infection, and co-morbid disorders.[1-4] Pain, however, is its predominant feature and the major complaint of patients throughout their life.[5-9] Sickle cell pain can be of mild, moderate, or severe intensity and is usually sharp or throbbing in nature, but can also be stabbing, deep, achy, lacerating, or shooting in quality.[5-9] Pain that is of mild or moderate intensity is usually treated at home with oral or topical analgesics plus certain non-pharmacological modalities.[5-9] Severe pain, however, often requires emergency room and/or hospital in-patient treatment with parenteral opioids. There are only rare multicenter randomized controlled trials that compare the effect of drug treatment on the length of hospital stay for painful crises in adult patients with SS.[10,11] Anecdotes and reports from single institutions indicate the duration of hospitalization for an uncomplicated painful crisis in adult patients varies between 6 and 10 days.[12-15]

Nonopioid analgesics, adjuvants, topicals and oral opioids are often used during hospitalization in addition to parenteral opioids. The amount of opioids required by patients during hospitalization in order to achieve pain relief is often so high that it concerns some providers who are not familiar with sickle cell disease and, consequently, tend to under-treat patients with sickle cell pain. Some providers may refuse to prescribe high doses of opioids during hospitalization and often accuse patients of being malingerers, drug- seeking or even drug addicts.

To the best of our knowledge there are no multicenter randomized controlled trials in the literature that describe the amount of opioids consumed by adult patients with SS at home and during acute painful episodes that are treated as outpatients or during hospitalization. Reports from single institutions described the utilization of NSAIDs alone or in combination with certain opioids in a relatively small number of hospitalized adult patients.[16,17] Another small study compared the utilization of parenteral butarphenol with morphine in adult patients in the emergency room.[18] Other reports addressed the factors that affect the quality of pain management in sickle cell disease (SCD).[19-21] The Multicenter Study of Hydroxyurea (MSH) in SS[22] gave us an

opportunity to report on this aspect of sickle cell disease. Although the original MSH study showed that hydroxyurea decreased the frequency of painful crises that required hospitalization, it did not address the duration of the painful crises or the amounts of opioids used to control crisis pain during hospitalization, and it did not differentiate between responders to HU and nonresponders. To that end, the goals of this paper are to (1) determine the hospital length of stay (LOS) of adult patients with SS enrolled in MSH 2) summarize the type and amount of opioids and other analgesics used by patients at home and during acute painful crises, and (3) compare the LOS and opioid utilization between the placebo and hydroxyurea treatment groups, and between treatment responders and nonresponders within the hydroxyurea group.

Methods

Patient characteristics

The methods of the MSH in SS have been described in detail elsewhere.[22] Briefly, MSH participants had to be at least 18 years old, with a diagnosis of SS, and at least 3 acute painful crises in the year prior to enrollment. A total of 299 patients were enrolled from 21 sites (20 in the United States and 1 in Canada). There were no significant differences between the hydroxyurea (HU) and placebo groups in terms of sex, race, age, or blood counts at baseline. The sample included roughly equal numbers of male (49%) and female (51%) patients, with an average age of 30 years (range 18-59) at study entry.

Measures

Data on opioid use came from three sources: a “Patient Diary” form covering two-week periods, completed daily at home by patients, and returned to clinical sites at follow-up visits; a “Follow-Up Visit” form, completed by physicians at regular follow-up visits every two weeks; and a “Medical Contact” form, completed by physicians whenever a patient presented for any medical contact other than the regular follow-up visits.

On the Patient Diary, patients indicated daily severity of pain and use of any analgesic (but not the specific analgesic or dosage). The patient diaries were used to determine overall frequency of at-home analgesic use. Analgesic frequency was defined as the proportion of all days on which patients reported using analgesics.

On the Follow-Up Visit form, physicians indicated use of any oral or transdermal opioid since the last visit and the specific opioids used, the total dosage (in mg) since the previous visit, and the number of days that the analgesic was taken. Physicians could indicate one or more of six opioids directly listed on the form (meperidine, oxycodone, morphine, hydromorphone, codeine, and the fentanyl patch) or write in others. The four most common write-ins were coded for this analysis (methadone, propoxyphene, levorphanol, and hydrocodone). The Follow-Up Visit form was used to

examine frequency of at-home analgesic use (as the proportion of all biweekly periods in which patients reported analgesic use), multiple analgesic use, and frequencies and dosages for specific analgesics.

On the Medical Contact forms, physicians indicated the location of each contact (in-patient, emergency facility, MSH clinic, non-MSH clinic, doctor's office, or 'other'). More than one choice could be marked if a single contact involved a visit to more than one type of facility. Physicians indicated use of specific analgesics from three categories: oral or transdermal opioids (meperidine, oxycodone, morphine, hydromorphone, codeine, and the fentanyl patch), parenteral opioids (meperidine, morphine, and hydromorphone), and non-steroidal anti-inflammatory agents (NSAIDs) (Ketorolac). The most common write-in oral opioids (hydrocodone and methadone) and parenteral opioids (nalbuphine and butorphanol) were also coded. Use of NSAIDs was uncommon and no write-ins were coded. Physicians indicated the total dose (in mg) for each medication and the number of days that medication was used.

Painful crises

Analysis of hospital length of stay (LOS) and of analgesic use during acute care and in-patient contacts was restricted to contacts defined as sickle cell-related acute painful crises under the criteria of the MSH clinical trial. In the trial, crises were defined as visits to a medical facility that lasted more than four hours for acute sickling-related pain, which was treated with a parenterally administered opioid (except for a few facilities in which only orally administered opioids were used).[22] Analyses were restricted to painful crises in order to exclude medical contacts that might not be related specifically to sickle cell pain or to other complications of the disease or comorbid disorders.

Painful crises were divided into two categories: those involving in-patient hospitalization and those involving only acute care facilities. If a crisis included in-patient hospitalization, regardless of contact with another type of facility, it was coded as in-patient. If the crisis involved only an outpatient acute care facility (ER, MSH clinic, non-MSH clinic, or doctor's office), it was coded as acute care. In all subsequent analyses, these categories were examined separately. The Medical Contact Form

provided data on the overall frequency of analgesic use, multiple analgesic use, and the frequencies and dosages for specific analgesics, during painful crises.

Treatment group assignment and hydroxyurea response

Assignment to the HU or placebo group at study entry was a key predictor of interest for analgesic usage. HU recipients were also divided into responder and nonresponder groups, based on fetal hemoglobin (HbF) levels at baseline and at approximately 18 months after initiation of treatment. A responder was defined as any HU recipient whose baseline percentage of HbF was < 15%, but whose follow-up level was >= 15%. This definition was based on previous research suggesting that 15% fetal hemoglobin is a level expected to produce clinical benefits [23,24], and this level is defined by NHLBI treatment guidelines as a desired treatment outcome.[25] Thus, an increase of this magnitude in HbF could reasonably be expected to produce clinically salutary benefits.

Statistical Methods

Types and dosages of at-home, acute care, and in-hospital analgesic usage were explored descriptively. Frequencies of use for each analgesic were expressed in three ways: as (1) percentages of all at-home periods, acute care crises, and in-patient crises, (2) percentages of only those periods that involved analgesic use (for at-home use only), and (3) percentages of the total number of analgesics used across all at-home periods, acute care, and in-patient crises.

Equianalgesic doses were computed for each opioid, using standard formulas to convert doses into morphine equivalents.[6] For painful crises, total dosages for each opioid were converted to morphine equivalents and summed to get a single total dosage. Average daily doses were calculated by dividing the total dose by the number of days that the crisis lasted. When the crisis duration was less than one day, the number of days was set to one.

For at-home use, total dosages reported for each opioid on the Follow-up Visit form were converted to equianalgesic doses and summed to get an overall total. To

obtain daily averages, total doses were divided by the number of days of analgesic use reported on the Patient Diary corresponding to that Follow-Up Visit form. Total days of use were obtained from the Pain Diaries rather than the Follow-up Visit forms because data for days of use were much more complete in the Diaries. Patient diaries and Follow-Up Visit forms were matched using codes for visit number that appeared in the data file for each form.

A check on data distribution indicated extreme non-normality (high skewness and kurtosis) for variables related to equianalgesic dosing. All equianalgesic dosing variables were transformed using the natural logarithm to normalize data distributions. The log-transformed values were used for group comparisons in the modeling described below; least squares means (LSM) estimates from the models were exponentiated to convert LSM estimates back into units of mg morphine equivalent. The same procedure was used for data on the number and duration of painful crises.

The effects of treatment group and HU response on analgesic usage were examined through between-group comparisons of (a) the proportion of all diary days with analgesic use, (b) the occurrence of any analgesic use during at-home follow-ups, acute care crises, and in-patient crises, (c) the total number of different analgesics reported for each at-home follow-up, acute care, and in-patient painful crisis, (d) the total (two-week) and average (daily) equianalgesic doses used at home, (e) the daily equianalgesic doses used during acute care and in-patient painful crises; (f) cumulative dosing across at-home follow-ups and painful crises for each patient; and (g) the frequency, average duration, and cumulative duration of acute care and in-patient painful crises.

Group differences in the proportion of diary days with analgesic use were tested with linear regression models. Differences in analgesic use at home and use of parenteral and oral opioids and NSAIDs during painful crises were tested with Rao-Scott adjusted chi-square analyses (to control for multiple observations of each patient). Total analgesics used during each at-home follow-up and painful crisis were compared with Wilcoxon rank-sum tests with adjustment for clustering (to control for multiple observations of each patient). Differences in average and cumulative equianalgesic

dosing at home and during painful crises, and average and cumulative duration of painful crises, were tested with repeated-measures linear mixed models. Finally, frequency of acute care and in-patient painful crises were modeled with zero-inflated Poisson regression, due to large proportions of zeros and non-normality of the data. Results were considered statistically significant if the associated p-value was $\leq .05$, and 'marginally significant' if $.05 < p \leq .10$.

In light of the number of comparisons tested, the suggested thresholds for statistical significance ($p < .05$) and marginal significance ($0.05 < p < 0.10$) are intended only as a rough non-conservative guideline for all the post hoc analyses performed in this manuscript.

Results

Type and frequency of analgesic use at home

Overall frequency. Patients' average length of time in the MSH trial was 790 days (2.16 years). Based on the Patient Diaries, the mean and median percent of days with analgesic use were 39.9% and 35.0%, respectively, with a range from almost 0% to over 99% of all days. Of 16818 biweekly follow-up visits, oral opioid use was reported in 59.9% (this does not imply analgesic use on all days of each two-week follow-up period).

Frequency of individual analgesics. Table 1 lists the frequency of use for each opioid as a percentage of (a) all biweekly follow-up visits (n=16818); (b) only those visits for which opioid use was reported (n=10071); and (c) the total number of opioids reported (the sum of separate opioids from follow-up form; n=11302). Oxycodone and codeine were used most often, at 23% and 18% of all two-week follow-ups, respectively. Together they accounted for 61.7% of all analgesics used and were at least three times as frequent as the next most common opioids (meperidine and hydromorphone). Figure 1 displays frequency of use and mean dose (before equianalgesic transformation) for each oral opioid at home.

Equianalgesic dosing. The mean total dose during periods when analgesics were used was 219.6 (SD=480.69) mg morphine equivalent; the median was 112.5 mg morphine equivalent. For those days on which analgesics were used, the mean and median daily doses were 25.1 (SD=40.79) and 15 mg morphine equivalent, respectively. Because analgesics were typically not used every day, the average two-week total is not simply a multiple of the average daily dose.

Relationship of treatment assignment and treatment response to at-home analgesic use

Frequency of at-home use. Based on Patient Diaries, placebo patients used analgesics on 42.0% of all days, compared to 38.0% for hydroxyurea patients; however, this difference was not statistically significant. The difference in use of any analgesic during biweekly periods was also nonsignificant (58.8% for HU and 59.7% for placebo).

There was no significant difference between treatment groups in the use of multiple analgesics.

HU responders, however, used analgesics on significantly (p=.005) fewer days (22.6%) than either nonresponders (42.2%) or placebo patients (42.0%). HU responders also used analgesics during significantly fewer two-week periods (40.8%) than either nonresponders (63.3%) or placebo patients (59.7%), p=.006. When compared for use of multiple medications, responders used fewer than either nonresponders or placebo patients ($p<.0001$).

Equianalgesic dosing during at-home use. Table 2 summarizes least squares means (LSM) estimates from the mixed models of daily and two-week at-home dosing. The HU and placebo groups did not significantly differ in average daily dosing at 11.3 and 11.5 mg morphine equivalent, respectively, $p=.89$. For two-week total doses, the HU and placebo groups again did not significantly differ ($p=.60$).

For treatment response, average daily dosing for HU responders and nonresponders did not differ, at 11.1 and 11.4 mg morphine equivalent, respectively ($p=.98$). For two-week total doses, the difference in mean values was again not statistically significant ($p=.18$). However, the median value for two-week total dose is far lower for responders (45 mg) than nonresponders (135 mg), reflecting use by responders on significantly fewer days; variation in two-week totals was large (even after log transformation) and may have prevented the group difference from reaching significance.

Type and frequency of analgesic use during acute care (outpatient) contacts

Overall frequency. There were 2249 acute care contacts, not leading to in-patient hospitalization, that were defined as painful crises. Of these, 95.5% reported treatment with parenteral opioids, 10.9% with oral opioids, and 9.2% with NSAIDs (the three categories sum to more than the 100% because of multiple analgesic use by some patients).

Frequency of individual analgesics. Table 3 shows frequency of use of analgesics during painful crises. The most frequently used parenteral opioid was

meperidine, at 69.3% of contacts; hydromorphone was second, at only 14.3% of contacts. The most common oral opioid was oxycodone, at 3.9% of contacts. Figures 2 shows the percent of all acute care crises during which each parenteral opioid was used.

Dosing. During acute care crises with analgesics use, mean and median daily doses of parenteral opioids were 33.9 (SD=33.93) and 26 mg morphine equivalent, respectively. For crises with oral opioid use, mean and median doses were 29.8 mg (SD=45.23) and 15 mg morphine equivalent, respectively.

Relationship of treatment assignment/response to acute care analgesic use.

Frequency of acute care use. Placebo and HU patients did not differ in use of parenteral opioids (p=.90), oral opioids (p=.60) or NSAIDs (p=.53).

HU responders were more likely than nonresponders or placebo patients to use NSAIDs during outpatient acute care contacts (43.2% of contacts versus 6.6% and 10.0%, respectively), p<.0001; however, use of oral and parenteral opioids did not differ.

There were no differences in the total number of different analgesics used during acute care painful crises, either between treatment groups (p=.90) or between treatment response groups (p=.77).

Equianalgesic dosing during acute care painful crises. Results of mixed modeling for daily dosing are reported in Table 4. LSM estimates for treatment groups did not significantly differ for either oral dosing (p=.18) or parenteral dosing (p=.93). Response groups also did not significantly differ in either parenteral dosing (p=.41) or oral dosing (p=.60).

Type and frequency of analgesic use during in-patient painful crises

Overall frequency. There were 2209 painful crises involving in-patient hospitalizations. Of these contacts, 96.4% reported use of parenteral opioids, 47.7% oral opioids, and 11.3% NSAIDs.

Frequency of individual analgesics. Table 3 shows frequency of use for specific analgesics during in-patient crises. The most frequently used parenteral opioid was meperidine, at 75.3% of crises; morphine was second at 19.0%. The most common

oral opioid was oxycodone (at 19.6% of in-patient crises), with all others less than half as frequent. Figures 2 shows use of each parenteral opioids as a percent of all in-patient crises.

Medical inpatient contact dosing. The mean and median daily doses of parenteral opioids (when used) were 95.9 mg (SD=203.4) and 67 mg morphine equivalent, respectively. For crises involving use of oral opioids, mean and median doses were 75.2 mg (SD=182.93) and 40 mg morphine equivalent, respectively.

Relationship of treatment assignment /treatment response to in-patient analgesic use.

Frequency of hospital contact use. HU and placebo patients did not significantly differ in use of parenteral opioids (p=.71), oral opioids (p=.57) or NSAIDs (p=.26). Similarly, responders and nonresponders did not significantly differ in use of parenteral opioids (p=.73), oral opioids (p=.64), or NSAIDs (p=.48). Finally, neither the treatment groups nor the response groups differed in total analgesics used during in-patient contacts, p=.75 and p=.84, respectively.

Equianalgesic dosing during in-patient painful crises. Mixed model results for daily parenteral and oral dosing, by treatment and response groups, are reported in Table 4. LSM estimates of dosing indicate nonsignificant differences between treatment groups for both parenteral (p=.80) and oral (p=.96) use. There were also no significant differences among HU responder, nonresponder, and placebo patients in estimates of parenteral dosing (p=.71) or oral dosing (p=.43). Notably, median values for parenteral and oral dosing, and to a lesser extent mean estimates for parenteral and oral dosing, are higher for responders than nonresponders. Responders were both fewer in number and had significantly fewer in-patient crises (see below) than nonresponders.

Differences in number and duration of acute care and in-patient painful crises.

Previously, it has been shown that HU patients in MSH had a significantly lower rate of painful crises than did placebo patients[22]. We examined differences separately for acute care and in-patient painful crises, and between HU responders and nonresponders as well as treatment groups. Table 5 shows mean and median values

for the numbers of acute care and in-patient painful crises by treatment group and response group, and the mean and median duration of in-patient painful crises.

Number of in-patient and acute care crises. All models controlled for duration of patients' participation in the study. There was a significant difference between hydroxyurea and placebo groups in the number of in-patient painful crises (p=.0015), with fewer crises for hydroxyurea patients than for placebo patients. When divided into HU responders and nonresponders, differences were again significant (p<.0001), with the HU responders having significantly fewer in-patient crises than the nonresponders. Regression modeling also showed a significant difference between treatment groups in the number of acute care crises (p<.0001) and between response groups as well (p<.0001), with fewer crises for hydroxyurea patients compared placebo patients and for responders compared to nonresponders.

Average duration of in-patient and acute care crises. When crises did occur, there were no significant group differences in the average duration of those crises. For in-patient crises, average duration did not significantly differ for either treatment groups (p=.74) or response groups (p=.45); for acute-care crises, average duration also did not differ between treatment (p=.76) or response (p=.96) groups. However, as shown in Table 6, the average duration of in-patient crises was almost two days shorter for HU responders than for either non-responders or placebo patients.

Cumulative duration of in-patient and acute care crises. We also examined cumulative duration of in-patient painful crises and acute care painful crises. For each patient, we calculated the total amount of time spent hospitalized and in acute care by separately summing the duration of all in-patient and acute-care crises for that patient. The cumulative values were then transformed using the natural logarithm to normalize the data. Mixed models were used to compare cumulative duration between treatment groups and between response groups.

For treatment groups, there were no statistically significant differences in dosing or duration for in-patient care. There were marginally significant differences for parenteral dosing during acute care (p=.10), with lower total doses for patients using

HU, and for the cumulative duration of acute care crises (p=.095), with less cumulative time for HU patients.

For response group comparisons, multiple significant differences emerged. Table 6 shows mean and median values for cumulative dosing and cumulative duration, by response groups. HU responders spent less cumulative time hospitalized (p=.022) and less cumulative time in acute care (p=.015); they also had the lowest doses of parenteral opioids during acute care crises (p=.015). These differences emerged despite extreme variation in the cumulative dosing and duration variables (see SDs in Table 7); large numerical differences in other values (such as in-patient parenteral dosing) may not have been statistically significant (even after log transformation) due in part to the large SDs.

Discussion

The insignia of sickle cell disease (SCD), in general, and sickle cell anemia (SS), in particular, is the recurrent acute painful crisis that often requires admission to the hospital through the emergency department and treatment with relatively large amounts of opioids for a lengthy hospital stay that may last, in some patients, over one week. [6,26-28] The duration of the acute sickle cell painful crisis and its management has been a conundrum of confusion punctuated with assumptions, suspicions, stigmatization, faulty accusations, under-treatment, occasionally over- treatment, barriers to quality comprehensive care, and disparities. The acute sickle cell painful crisis is the most common cause of hospitalization of patients with SS. Besides the acute and severe pain, the crisis is often associated with other complications of the disease including, among other thing, infection, acute chest syndrome, hyperhemolysis, and sudden death.[4,6,29-32] These serious complications associated with the painful crisis usually manifest themselves within 1-5 days after hospital admission when discharge from the hospital is imminent. The duration of the crisis and its management with opioids has been a subject of controversy for a long time. Most insurance carriers approve regular payments for the care of admitted patients with painful crises for 3 or 4 days unless a longer hospital stay is justified. Panepinto et al. [33] found that the overall average of the hospital length of stay in children with sickle cell painful crises was 4.4 days with older children having longer LOS. Ellison and Bouchner [34] found that the unadjusted mean ± SD of the LOS for the Medicaid children with SCD was 4.0 ±6.24 days compared to 3.0 ± 5.22 for patients with private insurance. These 3 to 4 days of hospital LOS is often applied to adult patients with SS *pari passu*. To that end patients may be discharged prematurely and about 16% of discharged patients are readmitted within one week after discharge and about 50% are readmitted within one month .[35,36] Moreover, Davis et al. analyzed National Inpatient Sample trends from 1989-1993, and found on average an estimated 75,000 hospitalizations per year of SCD children and adults, with lengths of stay less than 5 days for children and over 7 days for adults.[37] Limiting the LOS per diagnosis by Insurance carriers seems to encourage providers to discharge their patients prematurely- a practice that is invariably associated with hospital readmission within a short period after discharge [38] The MSH study gave us a great opportunity to fill

the gap of knowledge pertinent to the LOS and the amount of opioid and non-opioid analgesics consumed by patients with SS as outpatients and during hospitalization for acute painful crises.

The MSH data showed that patients on HU are admitted less often to the hospital than patients on placebo. Moreover, when patients who responded to HU are admitted to the hospital for a painful crisis, the chances are that they will stay 2 days less than patients not taking or not responding to HU. The reduction in the frequency of hospital admissions and the shortened length of hospital stay amount to significant savings per admission per patient as was described previously.[39] Using 2009 charges, savings amount to an estimated savings of about $27,000 per 7-day hospital admission per patient. [40] Thus, besides its beneficial effects on morbidity and mortality [41]due to SS, HU has significant financial benefits. It is unfortunate that HU is underutilized [28] in the management of patients with SS in view of the potential savings to the institutions taking care of patients with SCD and to Medical insurance providers.

The second important aspect of this study is that it provides important information about the amount of opioid and non-opioid analgesics used by patients as outpatients and during acute painful crises. At home patients with SS use opioid analgesics frequently with oxycodone and codeine being the most commonly opioids used followed by meperidine and hydromorphone. Patients reported in their diaries that they used opioids about 40% of the time and some used them almost daily. This is similar to the data reported in the PiSCES study. [8] The oxycodone used was the short-acting one, because at the time of the trial in 1992-1995, the controlled release opioids (MScontin and Oxycontin) were either not available or were not in common use. Patients who responded to HU showed three significant differences in comparison to nonresponders and placebo groups: 1) they used analgesics on fewer days at home; 2) they used analgesics during fewer of two-week follow-up periods; and 3) they used multiple medications less often than the other two groups. These findings suggest that HU seems to ameliorate the severity of painful episodes that occur at home.

HU, however, did not affect the use of any analgesic category during acute painful episodes treated as outpatients in the emergency department, clinic, medical office or

day unit. Responders to HU were more likely than nonresponders and placebo groups to use NSAIDs during these crises, but there was no difference in the use of parenteral or oral opioids. Again this may suggest that the pain intensity in these crises seems to be slightly milder in responders in comparison to nonresponders.

As was reported previously [22], HU decreased the frequency of painful crises by about 50%. The decrease in responders is even more impressive and amounts to about 75% reduction in the number of painful crises that require hospital admission. Moreover, the hospital length of stay is about 2 days shorter than nonresponders or placebo groups. The average daily amount of opioids used by the placebo group during hospitalization, however, is not significantly different from the responder and nonresponder groups. This suggests that the severity of painful crises during hospitalization seems to be the same during the initial days of the crisis in the placebo and HU groups. Responders may have been hospitalized only for the most severe crises while nonresponders were hospitalized more often and their hospitalizations may have included many milder crises. Since responders to HU are admitted to the hospital less frequently and their length of stay is about 2 days shorter per admission, the cumulative amount of opioids responders utilize over time is much smaller than that consumed by the placebo and nonresponder groups. The advantages of this reduction are not only financial but include the reduction of side effects associated with long term use of opioids including, among other things, tolerance, dependence and hyperalgesia. Thus HU decreases the frequency of hospital admissions due to crises, shortens their duration, decreases the frequency of acute chest syndromes and reduces the net amount of opioids utililized during hospitalization. Moreover, should hydroxyurea be approved for use in children the medical and financial benefits would be substantial.

Another aspect of this study that should be addressed pertains to the high utilization of meperidine during MSH. This was the drug of choice between the 1960's and 1990's and the preferred opioid by the majority of patients. One of the reasons is that the FDA approved meperidine for the treatment of severe pain in November 1942, whereas, morphine sulphate was approved in January 1984. The decline in the utilization of meperidine is due to the epileptogenic effect of normeperidine, its major metabolite. The use of meperidine for the treatment of sickle cell painful crisis continues to be

controversial.[42-44] There is consensus at the present that meperidine should not be used in patients with history of seizure or in the presence of renal impairment. The reported incidence of seizures due to meperidine varies between 1 to 12 %. [45,46] The disadvantages for morphine are that its utilization in patients with SCD seems to be associated with acute chest syndrome [47-48] and that it induces kidney injury in the transgenic sickle cell mouse.[49] The increase in acute chest syndrome could be incidental due to increased awareness among providers of the severity of pulmonary complications of SCD. Whether the advent of morphine sulphate has anything to do with this increase remains to be determined.

In Conclusion this study shows that the beneficial effects of treating sickle cell anemia with hydroxyurea include shortening the duration of hospitalization due to acute painful episodes and reducing the net amount of opioid utilization during hospitalization in addition to its known effects of reducing the frequency of hospital admissions due to crises,[22] reducing the frequency of acute chest syndrome,[22] improving the quality of life[50] and decreasing morbidity & mortality.[41,51]

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Authorship Contributions

SKB: Designed, planned and supervised the study, interpreted data and wrote the manuscript.

RLB: Performed all statistical data, analyzed and interpreted data, wrote Methods and results sections of the manuscript.

WFM: Analyzed and interpreted data, performed statistical analyses and edited the manuscript.

OLC: Interpreted data and edited the manuscript

WRS: Interpreted data and edited the manuscript.

MAW: Interpreted data and edited the manuscript.

Disclosure of Conflicts of Interest

Authors declare no conflict of interest (Signed forms pending)

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Tables

Table 1.
Frequency of at-home opioid use

Opioid	Frequency			
(listed in order of frequency)	% of all diaries (n=16818)	% of diaries with any opioid use[a] (n=10071)	Mean daily dose, mg (SD)[b]	Median daily dose, mg[b]
Any opioid	59.9	100.0	NA	NA
Oxycodone	23.2	39.1	15.5 (9.65)	12.3
Codeine	18.3	31.0	79.8 (77.24)	60.0
Meperidine	6.7	11.4	186.7 (190.70)	118.3
Hydromorphone	6.6	11.2	7.1 (5.21)	4.4
Hydrocodone	5.4	9.0	22.6 (18.98)	16.4
Morphine	3.3	5.6	40.2 (25.57)	30.0
Methadone	1.4	2.3	17.2 (10.34)	20.0
Propoxyphene	0.9	1.6	163.6 (79.15)	133.3

[a]Totals in this column sum to more than 100% due to multiple medication use at some visits.
[b] mg=milligrams, SD=Standard deviation. Values in these columns are the original dosage of each opioid, not the transformed equianalgesic dosages.

Table 2.
Equianalgesic dosing (mg morphine equivalent), at-home periods with any analgesic use

	[a]*Means(standard error)*		*Medians*	
	Two-week total dose	Average daily dose	Two-week total dose	Average daily dose
Treatment group				
Hydroxyurea (n=152)	59.7 (1.11)	11.3 (1.08)	114.0	15.0
Placebo (n=147)	64.4 (1.11)	11.5 (1.08)	112.5	15.0
HU response group				
Responders (n=27)	43.4 (1.28)	11.1 (1.21)	45.0	13.2
Nonresponders (n=116)	62.7 (1.12)	11.4 (1.09)	135.0	15.6

[a]Derived from least squares means (LSM) estimates in mixed models of log-transformed data. All values expressed as mg morphine equivalent.

Table 3.
Frequency and dosage in mg of opioid and NSAID use during painful crises

Analgesic	% of all acute care contacts[a] (n=2249)	Daily dose during acute care crises, mean (SD)[b]	Daily dose during acute care crises, median[b]	% of all in-patient contacts[a] (n=2209)	Daily dose during in-patient crises, mean (SD)[b]	Daily dose during in-patient crises, median[b]
Parenteral (any):	95.5	NA	NA	96.4	NA	NA
Meperidine	69.3	248.4 (145.70)	225	75.3	523.4 (382.40)	463
Hydromorphone	14.3	12.5 (9.26)	12	15.6	30.2 (65.26)	19
Morphine	8.9	18.8 (20.85)	14	19.0	53.3 (110.82)	30
Butorphanol	2.3	7.5 (4.81)	8	1.0	10.4 (12.45)	5
Nalbuphine	3.3	40.4 (14.84)	40	0.7	45.1 (23.3)	40
Oral (any):	10.9	NA	NA	47.7	NA	NA
Oxycodone	3.9	14.1 (11.34)	10	19.6	28.2 (23.47)	25
Meperidine	2.5	248.7 (311.52)	175	8.6	415.4 (303.22)	371
Hydromorphone	2.2	8.3 (4.80)	8	8.0	27.6 (96.73)	8
Morphine	1.1	62.0 (59.36)	60	7.9	143.1 (158.15)	90
Codeine	1.2	69.7 (43.94)	60	7.7	113.3 (72.82)	90
Hydrocodone	0.3	14.9 (11.73)	10	1.7	57.6 (182.41)	14
Methadone	0.5	27.4 (9.68)	30	1.6	39.3 (41.26)	28

[a]Totals for individual analgesics in a category sum to more than the category total due to multiple analgesic use at some contacts.
[b]Original doses of each drug (prior to conversion into mg morphine equivalent)
NA=Not applicable.

Table 4.
Daily equianalgesic dosing during acute care (outpatient) painful crises

	[a]*Means (standard error)*		*Medians*	
	Average daily parenteral dose	Average daily oral dose	Median daily parenteral dose	Median daily oral dose
Treatment group				
Hydroxyurea (n=152)	22.8 (1.07)	19.1 (1.10)	39.0	15.0
Placebo (n=147)	22.6 (1.06)	22.7 (1.09)	32.5	18.0
HU response group				
Responders (n=27)	17.7 (1.23)	16.0 (2.23)	13.0	16.0
Nonresponders (n=116)	23.5 (1.07)	20.2 (1.11)	39.0	16.0

[a]Derived from least squares means (LSM) estimates in mixed models of log-transformed data. All values expressed as mg morphine equivalent.

Table 5.
Daily equianalgesic dosing, in-patient painful crises

	[a]*Means (standard error)*		*Medians*	
	Average daily parenteral dose	Average daily oral dose	Median daily parenteral dose	Median daily oral dose
Treatment group				
Hydroxyurea (n=152)	42.7 (1.11)	34.0 (1.10)	74.8	42.0
Placebo (n=147)	41.3 (1.10)	34.2 (1.09)	63.6	43.3
HU response group				
Responders (n=27)	54.8 (1.40)	50.5 (1.38)	112.0	193.0
Nonresponders (n=116)	42.3 (1.12)	32.6 (1.10)	75.7	40.0

[a]Derived from least squares means (LSM) estimates in mixed models of log-transformed data. All values expressed as mg morphine equivalent.

Table 6
Number and duration of acute care and in-patient painful crises

	Number of acute care crises	Number of in-patient crises	LOS, in-patient crises
Treatment group	Mean (SD), median	Mean (SD), median	Mean (SD), median
Hydroxyurea (n=152)	6.6 (17.3), 2	6.4 (8.5), 3	7.6 (6.7), 6.0
Placebo (n=147)	8.5 (16.7), 2	8.5 (10.1), 5	7.8 (6.5), 6.2
HU response group			
Responders (n=27)	1.4 (2.9), 1	2.1 (4.1), 0	5.9 (2.6), 5.5
Nonresponders (n=116)	7.8 (19.4), 2	7.2 (8.8), 4	7.7 (6.8), 6.0

SD=Standard deviation, LOS=length of stay (in days).

Table 7.
Cumulative equianalgesic dosing and duration: means (SDs) by response group

	In-patient crises (n=2209)			Acute care crises (n=2409)		
HU response group	Cumulative parenteral dose in mg: mean (SD)	Cumulative oral dose in mg: mean (SD)	Cumulative duration in days: mean (SD)	Cumulative parenteral dose in mg: mean (SD)	Cumulative oral dose in mg: mean (SD)	Cumulative duration in hours: mean (SD)
Responders (n=27)	1114 (2770.4)	730 (2716.3)	12.4 (24.8)	35 (96.0)	0.6 (3.1)	27 (86.9)
Nonresponders (n=116)	3848 (9187.9)	736 (2624.6)	55.3 (75.1)	391 (1447.6)	26.6 (77.6)	108 (218.7)
Placebo (n=147)	4897 (15990.1)	1155 (5303.0)	66.2 (94.4)	459 (1203.6)	68.2 (256.2)	133 (260.9)

SD=Standard deviation, mg=mg morphine equivalent

Figure Legends

Figure 1. Utilization of oral opioids at home

Figure 2. Parenteral opioid utilization by crisis location

Figure 3. Oral opioid utilization by crisis location

Figure 4. Utilization of parenteral opioids in in-patient crises