**Title:** Adherence Outcomes of a Liquid Hydroxyurea Delivery Program in a Pediatric Population

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| **Abbreviation** | **Full term or phrase** |
| LHU | Liquid Hydroxyurea |
| Hb | Hemoglobin |
| MCV | Mean Corpuscular Volume |
| ACS | Acute Chest Syndrome |
| SCD | Sickle Cell Disease |
| VOE | Vaso-Occlusive Events |
| PDC | Proportion of Days Covered |
| BMC | Boston Medical Center |
| IRB | Institutional Review Board |
| ANC | Absolute Neutrophil Count |
| ED | Emergency Department |
| HbF | Fetal Hemoglobin |
| HbSS | Sickle Hemoglobin |
| HgSB0 | Sickle Beta Zero Thalassemia |
| HbSC | Hemoglobin Sickle C Disease |
| BMI | Body Mass Index |
| BABY HUG | The Pediatric Hydroxyurea Phase 3 Clinical Trial |
| TCD | Transcranial Doppler |

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**Abstract**

**Background:** Hydroxyurea remains underutilized in the pediatric sickle cell population despite its well-known efficacy in decreasing sickle cell complications and hospitalizations. Access to refills and liquid formulation remains a critical barrier to adherence to hydroxyurea regimens.This study was undertaken to determine the clinical impact ofhome-delivering compounded liquid hydroxyurea (LHU) to pediatric patients with sickle cell disease.

**Procedure/Methods:** A retrospective cohort study was conducted using electronic health records and pharmacy databases. Pediatric patients younger than 21 years of hydroxyurea initiation from March 2016 to July 2020 who received compounded LHU from Boston Medical Center Pharmacy were included. The primary outcomes of the study were drug adherence (assessed by evaluating the proportion of days covered), rates of acute care utilization, laboratory values, and growth metrics before and after enrolling in the LHU delivery program.

**Results:** The final cohort included 41 patients. Significant increases in hemoglobin 0.34 g/dl (95% CI: 0.04-0.63, p=0.02) and mean corpuscular volume 3.2 FI (95% CI: 0.92-5.4, p=0.007) occurred. Hospitalizations decreased by 51.3% (p=0.01), and acute chest syndrome episodes decreased by 86.4% (p=0.02) post-initiation of the LHU delivery program. Drug adherence had a median value of 0.95 one-year post-initiation of LHU.

**Conclusions: Home delivery of compounded LHU improved drug adherence, decreased hospitalizations, and improved laboratory outcomes in pediatric patients with sickle cell disease by overcoming barriers to access. Nationwide implementation of similar home delivery programs can significantly improve outcomes among pediatric patients with sickle cell disease.**

**Introduction**

Sickle cell disease (SCD) is the most common genetic disease in the United States, affecting approximately 100,000 individuals1. Mutations in the beta-globin gene promote sickling of erythrocytes, leading to vaso-occlusive episodes (VOEs), acute chest syndrome (ACS), and hospitalizations2–6. These events increase with age, leading to disability, decreased quality of life and life expectancy, and increased healthcare costs7–11. Therefore, treatment of SCD with hydroxyurea (HU), beginning at nine months, is an essential component of improving outcomes for pediatric and adult patients with SCD because it can decrease the frequency of VOEs, ACS episodes, hospitalizations, and transfusions, with few side effects12–14.

HU utilization and adherence rates remain significant barriers to treating pediatric SCD despite its efficacy. In 2015, there was an estimated HU use of 28% in the pediatric population15. Although use has increased since then, adherence rates, measured through the proportion of days covered (PDC)16, are reported to range from 48-80% in the pediatric population1717–20. Patient adherence rates vary due to lack of parent and patient engagement and understanding of side effects21, inability to attend frequent monitoring visits, transition to adolescence22, lapse in insurance coverage23, and lack of access to refills and different formulations of the drug24. Increasing adherence has focused on teaching25 and monitoring medication possession and administration using mobile applications22,26,27, with limited effect. These approaches have highlighted the challenges associated with increasing adherence and the fact that significant gaps remain underexplored in delivering and administering different formulations of HU in the pediatric population.

Given these gaps, a quality improvement project was established in 2016 at Boston Medical Center, an urban safety net hospital*,* to decrease barriers to the delivery and administration of HU. The program provided pediatric patients with at-home delivery of a compounded form of liquid HU (LHU) by coordinating with the in-house compounding pharmacy. These measures sought to improve adherence by decreasing barriers to obtaining HU, such as the inability to fill or pick up medications, and by providing HU in a liquid formulation, better tolerated by children than other HU formulations. We hypothesized that adherence, laboratory values, and clinical events would improve due to decreasing barriers to access. Here, we retrospectively assess the outcomes of this project and show the program’s capacity to achieve high adherence rates.

**Methods**

*Study design and data collection.*

Our study was IRB-exempt per the Boston University Medical Center IRB. Data was collected and deidentified by the authors after individual chart reviews. Data collected included demographics (sex, genotype, age, height, weight), laboratory values (fetal hemoglobin, total hemoglobin, absolute neutrophil count, mean corpuscular volume, reticulocyte count, bilirubin), pharmacological data (maximum dose of LHU tolerated, refill dates and periods), clinical outcomes (number of hospitalizations, number of emergency department (ED) visits, number of outpatient visits, instances of ACS and VOE), and patient and parent experiences.

Pre-laboratory values were collected on a date close to the LHU start date. Post-laboratory values were collected at least three months after the LHU start date and did not exceed one year after the date of initiation. Values were aggregated, averaged, and compared in the pre-and post-period.

Healthcare utilization values for hospitalizations, ACS episodes, VOEs, and outpatient visits were collected one year before and one year after the LHU start date. The average number of visits in the pre-and post-period (visits per year) was calculated and compared.

Patient experiences were collected through individual reviews of Hematology notes, and responses regarding the program from providers and patients were recorded and aggregated. Pharmacy data were used to calculate the proportion of days covered (PDC). The PDC is similar to the medication possession ratio but removes overlapping days between prescription refills, thus preventing inflated adherence measures. PDC was calculated as (sum of days covered in the period of investigation) ÷ (number of days in the period of the inquiry) × 100. Electronic health records of patients with a PDC<0.6 were reviewed to identify whether the gaps represented true non-adherence or appropriate treatment.

*Data analysis*

Pre- and post-LHU growth, laboratory, and hospital utilization data were analyzed using a two-tailed t-test. Data analysis was done using GraphPad Prism version 9.1.0. LHU prescribing information was obtained from the Boston Medical Center pharmacy.

**Results**

*Study design and patient population.*

A retrospective chart review was conducted on 59 patients in the LHU delivery program from March 2016 to July 2020. Eighteen were excluded because they were older than 21 years at the start of LHU, had confounding factors related to the COVID-19 pandemic, had HU prescribed through other pharmacies, or had unobtainable data (**Supplementary Figure 1, Supplementary Table 1**).

Forty-one patients were included in the data analysis (**Table 1**). The genotypes included were HbSS (n=39), HgSB0thalassemia (n=1), and HbSC (n=1). Sex distribution was equal (male 49%, female 51%). The median age at the time of LHU initiation was two years (IQR 0.75-5.5), with patients’ start age ranging from 0.75 (i.e., nine months) to 21 years. Of the 41 patients, 34% had prior HU exposure; 63% initiated LHU use through the Boston Medical Center pharmacy and had no prior HU exposure. The median HU dose tolerated was 22mg/kg/day (IQR 20-28.5), ranging from 15 to 36 mg/kg/day.

*The proportion of days covered.*

The median PDC was 0.94 (IQR, 0.91-0.99) at the time laboratory values were collected and 0.95 (IQR 0.91-0.99) one year after the initiation of LHU (**Figure 1A, 1B**). Upon review of the 1-year post-initiation data, one patient’s PDC denominator was adjusted because appropriate treatment gaps were identified. After accounting for appropriate therapy gaps, the final median PDC was 0.95 (IQR 0.91-0.99).

*Laboratory value outcomes of LHU delivery*

Growth metrics and laboratory values were collected before (pre) and after (post) initiation of LHU (**Table 2**). Height and weight percentiles increased during the pre- and post-period, both by 2.7%, although this was not statistically significant. Among the lab values assessed, hemoglobin increased by 3.9% (p=0.02), and MCV increased by 3.9% (0.007). Results for the remaining laboratory values were not significant (**Table 2**).

*Frequency of outpatient visits, ED visits, and hospitalizations*

We collected the total number of outpatient and ED visits and hospitalizations one year before and one year after the initiation of LHU (**Table 3**). Hospitalizations and ED visits were relatively uncommon; however, comparing the pre-and post-events revealed a decrease of 51.3% and 29.9% for each. The reduction in hospitalizations was statistically significant (p=0.01), whereas the decrease in ED visits was not (p=0.06). Outpatient visits did not significantly increase during the pre- and post-period.

*Frequency of acute chest syndrome and vaso-occlusive episodes*

ACS and VOE frequencies were calculated one year before and one year after initiating LHU. ACS was uncommon across patients, with a % relative decrease in ACS episodes of 86.4% (p=0.02). However, VOEs did not significantly decrease (p=0.09) across the group (**Table 3**).

*Patient experiences*

As part of the chart review, patients’ experiences were collected. Chart reviews were notable for the advantages and disadvantages of the LHU delivery program (**Supplementary Table 2**). Parents and clinicians noted cost, delivery, and difficulty tolerating capsules as barriers to access; these issues were resolved after switching to or initiating LHU delivery through the hospital’s pharmacy. Despite this improvement, barriers to access through the hospital’s pharmacy included difficulty with delivery and requesting prescription refills. Difficulty with deliveries was common for patients who were homeless. Difficulty with prescription refills was common for parents who did not understand that the pharmacy would automatically renew prescriptions after visits and had questions on how to obtain a refill.

**Discussion**

A liquid HU delivery program was established at the Boston Medical Center in 2016 to address gaps in the delivery of and adherence to HU regimens in pediatric patients with SCD. PDC measurements indicated over 90% adherence for most patients. Laboratory outcomes showed an expected increase in MCV14, a decrease in ANC values, and an increase in hemoglobin and fetal hemoglobin levels. Healthcare utilization metrics decreased for SCD-related emergencies after the initiation of LHU. Altogether, these suggest that the program decreased HU access and adherence barriers.

The primary aim of this study was to determine whether providing LHU directly to patients affected adherence measures. Importantly, our PDCs are significantly higher than reported previously18,19,17, highlighting that adherence increases when this medication is provided directly to the patient. This model also tackles other barriers to access reported by families, including insurance coverage/cost, delivery, and difficulty tolerating capsules. As our population included patients aged nine months to 21 years, these outcomes reinforced the need for better delivery measures and the provision of liquid formulations of HU, which are easier to administer and take in this population. Not all barriers were effectively overcome by this program, including education regarding automatic refills and difficulty with homelessness; nevertheless, these lingering issues did not affect the PDC.

A secondary aim of this study was to determine whether this program would affect laboratory values. The BABY HUG trial showed that hemoglobin increased by 3% (0.3 g/dL) for patients on HU and decreased by 7% (0.6 g/dL) for those on placebo14. Subsequent studies show a more considerable mean increase in hemoglobin of 1.3 g/dL23. Our study shows a mild increase of 0.34g/dL ± 0.91 (p=0.02) among our patients after initiating LHU. The mild improvement is consistent with previous studies. This could be explained by the fact that HU dose titrations lasted six months in the trial compared to our post-initiation values, which were recorded as early as three months for some patients. Additionally, 34% of our patients were not “naïve” to LHU; thus, maximal response to HU may have occurred at another point not captured by our data. Importantly, patients with a greater than one g/dL increase in Hg belong to the “naïve” group.

Besides affecting hemoglobin, HU also induces fetal hemoglobin (HbF), which reduces the intracellular concentration of sickled hemoglobin (HbS) and inhibits the formation of the sickle polymer, thus prolonging erythrocyte survival—changes in HbF percentages after HU initiation range from 3.2-15.5%23,28,29. In our study, fetal hemoglobin levels increased by 1.34% ± 6.4 (p=0.26) among all patients. Although not statistically significant, this could be due to our population composition (half of the patients were <4 years old at initiation of LHU (66%)), prior exposure to HU, and time of collection of laboratory values. In this younger population, high baseline levels of HbF combined with cumulative effects of naturally falling levels of HbF in the first years of life may blunt the rate of HbF increase by HU30*.* Also, HbF levels increase maximally by 26-40 weeks14,28, a point that may have been missed due to prior administration of HU or data collection before this time point. Similar patterns are notable in the MCV and ANC values, which show an expected increase and decrease, respectively. Overall, Hg and MCV values were noted to be significant, and patterns for all laboratory values are consistent with those in published data.

In addition to laboratory values, growth metrics were assessed pre and post-LHU initiation due to lower weight, height, and BMI in children with SCD due to higher hemolysis, anemia, inflammation, and increased metabolic rate31. The BABY HUG trial did not show any differences in height or weight among those who received HU31, but the HUG-KIDs study showed an increase in weight in males who received HU32. Thus, we assessed our population's absolute numbers and percentiles for height and weight. We noted no significant growth or weight percentile changes pre- or post-initiation of LHU. Inspection of absolute changes in height and weight showed no adverse effect on growth, consistent with findings of the BABY HUG and HUG-KIDs studies.

Previous studies have shown decreased ED visits and hospitalizations among children treated with HU14,30,33. We first assessed the numbers of outpatient visits, which were similar pre- and post-LHU initiation, suggesting adequate follow-up in our patient population. We then assessed ED visits and hospitalizations, which decreased frequency after LHU initiation. Given that ED visits and hospitalizations correlate with ACS and VOEs, a decrease in these events was also noted after LHU initiation. Despite the low incidence of these events in our population, the relative decline suggests that the LHU administration has aided in decreasing these events.

This study holds three main strengths. First, it describes the impact of an LHU delivery program at a large metropolitan hospital by reporting various SCD outcomes and providing adherence measures. Few published interventions to improve medication adherence in pediatric SCD exist. Such studies in children with SCD have noted nonadherence to moderate adherence to medication regimens20,23. Second, this study provides strong adherence measures correlating with laboratory values and healthcare utilization data. Third, we include patient experiences and anecdotally provide barriers to access for our patient population, thus providing points for improvement. Importantly, our data suggest that administering LHU through compounding pharmacies collaborating with the primary hematologist clinic, as done at Boston Medical Center, may help increase adherence.

The most notable limitation of our study is the small sample size. Since its inception, the program has enrolled 59 patients, 18 of whom had to be excluded from data analysis. As more patients are enrolled, extending the analysis to determine whether laboratory, healthcare utilization, and adherence findings hold will be beneficial. Additionally, given that the program’s inception was aimed at providing a more reliable alternative to delivering LHU to pediatric patients, a proportion of our patients (34%) had prior exposure to LHU. These patients were usually older and received HU from other compounding pharmacies before enrolling in the program. This prior exposure adds confounding factors to the outcomes analysis and necessitates assessment with a larger patient cohort. Other SCD outcomes that we could not report include blood transfusion requirements and TCD Doppler changes, which would also be beneficial to examine. Finally, our study population included 1 HbSC and 1 HbSB0 patient. Although confounding factors added by these patients were likely minimal, given their low representation, the impact of HU on these phenotypes cannot be fully assessed in this study.

In summary, our data highlights that delivery of LHU through our hospital’s pharmacy has various beneficial outcomes. Although our sample size is small, trends in Hb, HbF, MCV, and ANC values, decreased ED visits and adverse events, and high PDC indicates improved adherence after enrollment in this program. As this program continues to grow, these outcomes require further follow-up. However, the results from this study may apply to implementing programs in other communities and nations with a high SCD burden where safety net hospitals are available. Such programs would centralize prescribing and delivering medication to patients who may not have access to alternative formulations that are easier to administer in children, such as liquid HU, while ensuring that barriers such as cost, delivery, and navigating health care systems are overcome.

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