Paper # 2013

THE COST-EFFECTIVENESS OF HYDROXYUREA FOR SICKLE CELL DISEASE AMONG CHILDREN IN SUB-SAHARAN AFRICA

Mauricio Rodriguez, Donald Ayers, Chanchal Bashal, Peter Mallow, Paul Niklewski

Xavier University, Cincinnati, Ohio, United States

Background: Globally, the burden of sickle cell disease (SCD) disease is concentrated (75%) in Sub-Saharan, Africa (SSA). Mortality rates (50% to 90%) are high among children with SCD in SSA, due to limited resources. Reductions in complications associated with disease are well established with hydroxyurea (HU) use among children with SCD in SSA despite limited adoption of HU.

Objectives: To conduct a cost-effectiveness analysis (CEA) of HU treatment compared to standard of care (SOC) for children with SCD in SSA. The perspective of the analysis was the Angola Ministry of Health.

Design/Method: We developed a Markov model with microsimulation utilizing real-world data (RWD) obtained from the published literature. Heath state monthly transitions consisted of: SCD symptom free; vaso-occlusive; acute chest syndrome (ACS)/ pneumonia; blood transfusion; hospitalization; and a death state (final). Health utilities and costs were in quality-adjusted life years (QALYs) and United States Dollars (USD), respectively. Hypothetical patients had a starting date at birth and were followed for 10 years using a cycle time of one month. The willingness-to-pay threshold (WTP) was set at $20,000 USD. Outputs included, incremental cost-effectiveness ratio (ICER) of HU compared to SOC. A one-way sensitivity analysis was performed to assess uncertainty.

Results: HU was found to decrease costs -$3,628 and increase QALYs, 1.8 per patient compared to SOC from a total of 1 million simulated patients. This translated to an ICER of -$2,016/ QALY. Mean monthly times within the symptom free health state increased by 71% for HU compared to control, resulting in a reduction among deleterious health states: vaso-occlusive (-87%)*;* ACS/ pneumonia (-90%); transfusions (-94%); and hospitalizations (-95%). HU was expected to decrease costs and increase QALYs in 95% of simulated patients. A one-way sensitivity analysis varying costs of HU treatment by low, high, and neutral, all increased effectiveness by 1.8 QALYs and maintained the cost-effectiveness-ICERs (-$3,185/QALY; -$789/ QALY; and $86/ QALY), respectively.

Conclusion: HU was a cost-effective treatment, expected to reduce costs and increase QALYs, for SCD in Angola, Africa. HU treatment is a noninvasive modality that can improve survival and reduce complications associated with disease. Despite limited resources, investment in HU may have a substantial cost-effective impact on the mortality among newborns and children with SCD. Results from our analysis may help inform policymakers on resource allocation to reduce the burden of SCD.

Paper # 2014

EARLY HYDROXYUREA USE MAY BE NEUROPROTECTIVE IN CHILDREN WITH SICKLE CELL ANEMIA

Kristine Karkoska, Amanda Pfeiffer, Patrick McGann

Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, United States

Background: Sickle cell anemia (SCA)-related neurocognitive dysfunction begins early and affects executive functioning and attention. Evidence suggests hydroxyurea may be neuroprotective, but is limited to children who began therapy well after the onset of cognitive decline. In 2014, Cincinnati Children's (CCHMC) began treating children as young as six months; these children offer a unique population to evaluate the effects of the early introduction of hydroxyurea on neurocognition.

Objectives: To compare the neurocognitive status of children with SCA who initiated hydroxyurea before five years to an unaffected, matched cohort and to historically treated patients to assess whether hydroxyurea may be neuroprotective.

Design/Method: We completed a cross-sectional analysis of the neurocognitive status of our SCA population. Children >3 yo with SCA were enrolled in two cohorts: 1) children with SCA (HbSS or HbS-beta^{0}thalassemia) who began hydroxyurea <5 yo and 2) children with SCA who did not qualify for the first cohort (on hydroxyurea or chronic transfusions (CTT)). Unaffected controls (patients' siblings or from CCHMC primary care clinic) were matched to each child in the first cohort by age, race, and sex. All participants completed the NIH Toolbox: Cognition Battery, a shortened neuropsychological evaluation (mean 100, SD 15).

Results: We enrolled 30 patients into the first cohort with 31 matched controls (early hydroxyurea: mean age 7.2 +/- 3.1 years, 50% female). The traditionally-treated SCA cohort included 20 patients (mean age 15 +/- 5.1 years, 70% female). There were no differences in age, sex, patient or maternal education, and Area Deprivation Index (socioeconomic status) between the early hydroxyurea and control cohorts. The early hydroxyurea patients and controls scored no differently on the composite cognition (86 +/- 13 versus 87 +/- 14, $p = 0.6$); conversely, the early hydroxyurea patients scored significantly higher than the traditionally-treated cohort on the composite cognition (versus 77 +/- 14, $p = 0.03$). On a linear regression model, age ($p < 0.001$) and patient education ($p = 0.04$) were significantly correlated with cognition with all included. When limited to patients with SCA on hydroxyurea, age ($p < 0.001$) and patient education ($p = 0.006$) remained significant; maternal education ($p = 0.07$), hemoglobin ($p = 0.07$), and fetal hemoglobin ($p = 0.07$) approached significance.

Conclusion: Children with SCA are disproportionately at risk for poor academic performance from their disease process. If started early and maintained during brain development, hydroxyurea may be neuroprotective. Our data provide further evidence to support hydroxyurea's universal prescription for all children with SCA.

Paper # 2015

SURGICAL REVASCULARIZATION REDUCES STROKE RISK IN SICKLE CELL DISEASE AND MOYAMOYA SYNDROME

Philipp Aldana, Ricardo Hanel, Joseph Piatt, Sabrina Han, Corinna Schultz, Cynthia Gauger, Manisha Bansal

Wolfson Children's Hospital/University of Florida Jacksonville/Nemours Children's Health, Jacksonville, Florida, United States

Background: Cerebral revascularization surgery (CRS) is a widely used treatment to reduce stroke in patients with Moyamoya disease, an idiopathic progressive cerebral vasculopathy. Patients with sickle cell disease are known to develop moyamoya syndrome, which confers a high risk for stroke, despite chronic transfusion therapy. These patients have limited proven treatments options to reduce stroke. Recent studies have suggested that CRS may be a safe and effective therapy to reduce risk of cerebrovascular complications in patients with sickle cell disease and moyamoya syndrome (SCD-MMS) but have been limited by small sample size and lack of a control group.

Objective: To investigate whether revascularization surgery reduces the risk of cerebrovascular events (CVEs) in comparison to conservative management alone in a retrospective cohort of children with SCD-MMS.

Design/Method: Sickle Cell Disease Programs offerning both hematological and neurosurgical treatment were recruited. A retrospective review of data of patients with SCD-MMS ($\leq$18 y.o.) was performed. Detailed information on sickle cell disease course, stroke and surgical histories were extracted. The incidence of CVEs (stroke and TIAs) between patients treated with surgical revascularization was compared to those with conservative management alone. Multivariate regression models were generated and logistic regression analyses were performed.

Results: A total of 141 patients with SCD-MMS were studied. 78 (55.3%) were treated with conservative management and revascularization surgery (Surgery group) and 63 (44.7%) were treated with conservative management alone (Conservative group). Compared to the Conservative group, patients in the Surgery group had an earlier onset of moyamoya diagnosis, worse baseline mRS scores and a greater proportion of patients with a history of CVEs before the start of treatment. Despite these, patients in the Surgery group had reduced odds of developing a CVE over the duration of their risk period (odds ratio = 0.27, 95% CI: 0.08-0.94, P = .040). Furthermore, when comparing patients in the Surgery group during their pre-surgical periods and post-surgical periods, patients had markedly reduced odds of developing a CVE after surgery (odds ratio = 0.22, 95% CI = 0.08-0.58, P = .002). 7 patients (8.9%) developed adverse events related to surgery..

Conclusion: This multicenter retrospective study provides strong evidence that revascularization surgery can reduce the risk of CVEs, can be performed safely and is a viable treatment option to reduce stroke in patients with sickle cell disease and moyamoya syndrome. Prospective studies

will be needed to futher validate these findings.

Paper # 2016

THE CLINICAL RESPIRATORY SCORE: ASSESSING ACUTE CHEST SYNDROME SEVERITY RISK IN SICKLE CELL DISEASE

Shani Johnson Anum, Andy Yu, Jonathan Flanagan, Julie Katkin, Nicholas Ettinger, Saleh Bhar, Gladstone Airewele, Danielle Guffey, Venée Tubman

Baylor College of Medicine/Texas Children's Hospital, Houston, Texas, United States

Background: Acute chest syndrome (ACS) remains a leading cause of morbidity and mortality in children with sickle cell disease (SCD). The NHLBI-sponsored Comprehensive Sickle Cell Centers developed a clinical severity index (CSI) to retrospectively classify the outcome of an episode of ACS by clinical features and interventions needed. At our institution, a clinical respiratory score (CRS) was developed for monitoring hospitalized patients with SCD with or at risk for ACS. The CRS ranges from 0-12, and is determined by a set of objective clinical findings. Per our clinical algorithm, a CRS ≥4 warrants consideration of ICU transfer. During an ACS episode, it would be useful to have a clinical tool that could predict severe ACS. The utility of the CRS in predicting the severity of an episode of ACS has not been established.

Objectives: To identify the relationship between an institution-developed CRS and the CSI. We hypothesize that there is a significant association between pediatric patients with ACS who have peak CRS ≥4 during a hospitalization and having an outcome of severe of worse per the ACS CSI.

Design/Method: We performed a retrospective chart review of patients with SCD (any genotype) admitted to Texas Children's Hospital with ACS between 2015 and 2021. Patients were aged 3-21 years, had ICD-10 codes related to ACS, and had documented CRS scores. Peak CRS was defined as the maximum CRS during admission. CSI designations were converted into a numeric score: Mild = 1, Moderate = 2, Severe or Very Severe = 3. CRS and CSI scores were analyzed using Chi-squared and simple regression tests.

Results: We identified 205 patients who met inclusion criteria. The mean age was 10.5 years (SD 4.9), 55.1% were male, 89.8% identified as Black/African American, and 8.3% identified as Hispanic. Mean and median CRS for the cohort were 1.5 (SD 1.4) and 1.0; mean and median CSI were 1.7 (SD 0.6) and 2.0. There was a significant association between peak CRS ≥4 and a CSI = 3 (OR 8.82 [95% CI 2.87 – 24.24], $p < 0.001$). Similarly, there was a statistically significant, but weak correlation between peak CRS and CSI scores across the population (r^2 0.22 [95% CI 0.16 – 0.27], $p < 0.001$).

Conclusion: Peak CRS during an ACS admission is associated with ACS outcome (CSI), and a CRS ≥4 may suggest an increased risk of severe or very severe ACS. Patients with CRS ≥4 may warrant additional interventions to prevent severe outcomes.