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Long Term Effects of Hydroxyurea on Adult Patients with Sickle Cell Anemia

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ABSTRACT

The purpose of this evidence based practice literature review is to research the long term effects of the medication hydroxyurea on adult patients who have severe sickle cell disease and investigate if this medication improves overall health. The database utilized was CINAHL with the search parameters including: sickle cell disease, hydroxyurea, research and adults which led to the articles that were referenced in this paper. Based on the analysis and synthesis of the literature, hydroxyurea was found to have similar beneficial results that were statistically significant for patients with severe sickle cell disease. These articles utilized a variety of methods including two experimental and three non-experimental studies. The critical appraisal of the research supports the use of hydroxyurea for adults with severe sickle cell disease demonstrating fewer acute and chronic complications.

BACKGROUND

In the United States, about 50,000 Americans of African descent have sickle cell disease (Platt, 2008). This illness is very painful and these patients have increased risk of morbidity and mortality (Ballas et al., 2010; Ferguson, Arun, Carter, Walker, & Castro, 2002; Platt, 2008; Smith et al., 2011; Steinberg et al., 2003; Voskaridou et al., 2010). Morbidities commonly seen in patients with sickle cell are pain crises, hospitalizations, blood transfusions, strokes, acute chest syndrome, chronic lung disease, avascular necrosis, leg ulcers and premature death (Platt, 2008). Hydroxyurea is the only medication available that slows down or prevents sickling of the red blood cells by increasing the amount of hemoglobin F (HbF) in the blood (Ballas et al., 2010; Smith et al., 2011; Voskaridou et al., 2010). National Institutes of Health Consensus Development Conference has created a national guideline that hydroxyurea should be utilized for sickle cell disease (Brawley et al., 2008). Although this is the only medication available and there is a national guideline explaining its benefits, many advanced practice nurses are not utilizing it to its fullest potential.

Reasons for underutilization might include confusion and lack of knowledge about hydroxyurea by the practitioners, patients, their families and community. Hydroxyurea is considered an antineoplastic agent and can be used for sickle cell disease and for some cancers. It comes as a capsule, is taken about the same time daily and can take up to three months for the medication to reach its full clinical response. The medication can have some side effects including nausea, vomiting, diarrhea and constipation (MedlinePlus, 2012). Because this medication needs to be taken daily, has side effects and is considered a chemotherapeutic agent, this can lead to noncompliance among patients.

There are also socioeconomic factors and health disparities relating to the African American population that could affect administration. Many patients in underserved areas may

not receive adequate health care relating to their sickle cell disease. If they do not receive adequate care then they are not receiving appropriate education regarding hydroxyurea. Consequently, noncompliance may result leading to increased risk for morbidity and mortality. This can lead to increased health problems and higher health care costs which negatively affects the patients, their families and communities. Advance practice nurses need to be current on the latest advances in health care in order to be advocates for adult patients with sickle cell disease.

ANALYSIS

In this literature review, five studies were reviewed. All of the studies had similar purposes of evaluating the effects of hydroxyurea on adult patients with sickle cell disease and all had similar hypotheses that beneficial results would be found with taking hydroxyurea compared to not taking hydroxyurea (Ballas et al., 2010; Ferguson et al., 2002; Smith et al., 2011; Steinberg et al., 2003; Voskaridou et al., 2010).

Ballas et al. (2010) investigated the efficacy of hydroxyurea on length of stay for hospitalizations, amount of hospitalizations and acute care visits, and analgesic use during hospitalizations, outpatient acute care contacts and at home. It compared these results between the placebo treatment group and hydroxyurea group and between the participants that responded to hydroxyurea and those that did not respond. Participants taking hydroxyurea were considered a responder to the treatment if their fetal hemoglobin (HbF) was <15% prior to hydroxyurea treatment and $\geq 15\%$ at 18 months after treatment. This experimental study included 299 participants from the Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH) that was conducted from 1992-1995. All participants had sickle cell disease with at least three painful crises a year. Participants were randomly assigned to receive a placebo or receive hydroxyurea. These patients were enrolled from 21 sites including 20 sites from the United States and 1 site from Canada. The ages of the participants enrolled ranged from 18 years old to 59 years old

with a mean age of 30 years old when the study began. About 49% of the participants were male and about 51% female. The average length of time in this study for participants was 2.16 years.

These results were evaluated with multiple tests including: least square means, linear regression models, Rao-Scott adjusted Chi-square analyses, Wilcoxon rank-sum tests, repeated-measures linear mixed models, and zero-inflated Poisson regression. Analgesic use was utilized at home on 22.6% of days with participants that responded to hydroxyurea, 42.2% for nonresponders and 42% for the placebo group, P value = 0.005. Analgesic use at home during two-week periods was utilized 40.8% for responders, 63.3% for nonresponders and 59.7% for placebo group, P value = 0.006. When comparing multiple medications, responders used less than nonresponders and placebo group, P value = <0.0001. The average daily dose for morphine at home was 11.3 mg for participants taking hydroxyurea compared to 11.5 mg for placebo participants, P value = 0.89. In a two week period of total doses, the participants taking hydroxyurea and the placebo did not significantly differ, P value = 0.60. The average daily dose for morphine at home with the hydroxyurea responders was 11.1 mg and 11.4 mg for the nonresponders, P value = 0.98. In a two week period of total doses, the participants that did and did not respond to hydroxyurea was not statistically significant, P value = 0.18.

Participants in the placebo and hydroxyurea group in acute care visits had similar use of parenteral opioids, P value = 0.90, oral opioids, P value = 0.60 and NSAIDS, P value = 0.53. Participants that did respond to hydroxyurea used NSAIDS during outpatient acute care visits 43.2% of contacts, nonresponders 6.6% and placebo group 10.0%, P value = <0.0001. No difference in the total number of analgesics used during acute care painful crises were found between the hydroxyurea and placebo group, P value = 0.90 or between the responder and nonresponders, P value = 0.77. Participants from the placebo and hydroxyurea group did not

have a significant difference in oral dosing, P value = 0.18 or parenteral dosing, P value = 0.93, during painful crises. The different response groups also did not have a significant difference in oral dosing, P value = 0.60 or parenteral dosing, P value = 0.41, during painful crises.

Participants in the placebo and hydroxyurea group while inpatient had similar use of parenteral opioids, P value = 0.71, oral opioids, P value = 0.57 or NSAIDS, P value = 0.26. The different response groups while inpatient also had similar use of parenteral opioids, P value = 0.73, oral opioids, P value = 0.64, or NSAIDS, P value = 0.48. All participants had similar total analgesic use while being inpatient with the different treatment groups, P value = 0.75 and the different response groups, P value = 0.84. Participants in the different treatment groups while inpatient did not have a significant difference in parenteral dosing, P value = 0.80 or oral dosing, P value = 0.96. Comparing the hydroxyurea responders, non responders and placebo group, there was also not a significant difference in parenteral dosing, P value = 0.71 or oral dosing, P value = 0.43.

Participants in the placebo and hydroxyurea groups had a significant difference in the number of inpatient painful crises with the hydroxyurea group having less crises, P value = <0.00015. Participants that responded to hydroxyurea compared to nonresponders also had a significant decrease in inpatient painful crises, P value = <0.0001. Participants in the placebo and hydroxyurea groups had a significant difference in the number of acute care crises, P value = < 0.0001 and between response groups, P value = < 0.0001. There was not a significant difference in average length of inpatient crises for the different treatment groups, P value = 0.74 or for the different response groups, P value = 0.45. However, the average length of stay during inpatient crises is two days less for hydroxyurea responders compared to nonresponders and placebo participants. There was also not a significant difference between average length of acute

care crises for the different treatment groups, P value = 0.76, or for the different responder groups, P value of 0.96. This study had multiple different variables that were tested with some being statically significant while others were not. This study is viewed as a level I because it utilizes an experimental design and has a quality of 2 and because there is moderate evidence to support the effectiveness of hydroxyurea, its strength is a B.

Ferguson et al. (2002) examined the effectiveness of hydroxyurea by measuring the number of hospitalizations and blood transfusions between participants that did and did not receive hydroxyurea. This study was an observational (nonexperimental) retrospective chart study that reviewed the records of 60 patients treated at the Howard University Center for Sickle Cell Disease in Washington, D.C., and the hematology/oncology ambulatory center of Union Memorial Hospital in Baltimore. The patients ranged in age from 19 years old to 58 years old with their mean age being 34.3 years. Twenty-two of the participants were men while the other were women. All participants included in this study had completed at least three months of hydroxyurea therapy. Thirty of the patients received hydroxyurea for 24 months while 30 had not, with their average amount of treatment to be 9.8 months.

These results were examined using Microsoft Excel 977. Hospital admissions overall declined from 1.12 per quarter before taking hydroxyurea to 0.85 per quarter after taking hydroxyurea, P value = 0.17. Blood transfusions overall decreased from 1.34 per quarter to 1.00 per quarter, P value = 0.25. The participants that had taken the hydroxyurea for at least 24 months had a decline from 0.83 hospital admissions per quarter to 0.58, P value = 0.04 and transfusions decreased from 1.22 per quarter to 0.51, P value = 0.07. The patients that received the hydroxyurea for at least three months had a decrease of hospital admissions per quarter from 1.43 to 0.91, P value = 0.49 and transfusion requirements did not change. The patients that

received hydroxyurea for four years had hospitalizations decreased from 0.89 per quarter to 0.60, P value = 0.23 and transfusions decreased from 2.16 to 0.75, P value = 0.07. This study is considered a level III due to it being a non-experimental study, has a quality of 5 and because the results show moderate evidence to support the effectiveness of hydroxyurea, its strength is a B.

Smith et al. (2011) measured the daily pain intensity ratings, daily analgesic use, daily pain-related utilization and amount of fetal hemoglobin (HbF) that was in the blood for patients who were and were not taking hydroxyurea. This experimental study included 299 people from the MSH trial. The criteria for inclusion included people who had sickle cell disease and at least three painful crises a year. Participants were randomly assigned to receive a placebo or hydroxyurea. Ninety-five percent of the participants were African American and the remaining 5% was unknown. These patients were enrolled from 21 sites including 20 sites from the United States and 1 site from Canada. The ages of the participants enrolled ranged from 18 years old to 59 years old with a mean age of 30 years old when the study began. Almost half of the participants had completed at least some college, 61% were unemployed and 70% had a personal income of less than \$10,000 a year.

These results were examined with Pearson correlations and also mixed models regression analyses. It was supposed to last two years but stopped early because of the beneficial results that were seen. In the study, 134 of the 299 participants completed the full 2 years of follow-up with the mean follow-up being 21 months. Patients taking hydroxyurea had lower pain intensity, P value = 0.0007, had lower analgesic use, P value = 0.0006 and lower rates of acute visits, P value = <0.0001. There was an increase in HbF for participants that took hydroxyurea compared to placebo, P value = <0.0001. The higher increase in HbF showed lower pain, P value = <0.0001, lower need for analgesia, P value = <0.0001 and lower amount of acute visits, P value =

<0.0001. This study is viewed as a level I because it utilizes an experimental design and has a quality of 2 and because there is strong evidence to support the effectiveness of hydroxyurea, its strength is an A.

Steinberg et al. (2003) evaluated the efficacy in hydroxyurea treatment by measuring mortality rates and compared them to hemoglobin, HbF, neutrophils, absolute reticulocyte counts, and serum creatinine in patients with sickle cell anemia that did and did not receive hydroxyurea. This study was an observational (non-experimental) follow-up for up to nine years of the 299 patients that were in the MSH trial. Patients were enrolled from 21 sites including 20 sites from the United States and 1 site from Canada. The participants had to have at least three painful crises in the past year to be considered for this study.

These results were examined with multiple tests including: χ^2 , mean, standard deviations, equation logistic models, SAS v7.6, and Kaplan-Meier survival curves. Results from this study for up to 9 years included 233 participants of the 299 that had enrolled in the follow-up study. Prior to treatment, patients who had HbF lower than 0.5 g/dL had a 32% mortality rate at nine years compared to patients with HbF greater than 0.5 g/dL with a 15% mortality rate, P value = 0.01. Neutrophil counts above or below 5000/mm³ did not show any change in mortality, P value = 0.7. Patients with absolute reticulocyte counts less than 250000/mm³ and hemoglobin concentrations lower than 9 g/dL had increased mortality after 9 years with 38% dead at nine years, P value = 0.02. These same patients had lower HbF levels which were 0.42 g/dL vs. 0.2 g/dL, P value = 0.005. Patients had a higher mean serum creatinine levels of 1.49 mg/dL vs. 0.96 mg/dL, P value = 0.02. Patients with the lower scores received less hydroxyurea compared to the patients with the higher scores. Patients with no episodes of acute chest syndrome had a mortality of 18% while patients who had 1 or more episodes had a 32%

mortality rate , P value = 0.02. Patients who had three painful events a year had a mortality rate of 17% compared to the patients with more than three painful events who had a mortality rate of 27%, P value of 0.06. Death rates were reduced 40% during 3-month intervals when patient were taking hydroxyurea, P value = 0.04. This study did not explain if they considered any of the data statistically significant. However, the authors did state that their data should be interpreted cautiously because some of the patients taking hydroxyurea may also have had more medical care and better follow-up compared to patients that did not take the medication. This study is considered to be a level III due to it being a non-experimental study, has a quality of 5 and because the results show moderate evidence to support the effectiveness of hydroxyurea, its strength is a B.

Voskaridou et al. (2010) measured the number of hospitalizations, severe painful crises, transfusion rates, acute chest syndromes, blood levels of hemoglobin, HbF, leukocytes, platelets, reticulocytes, serum bilirubin, LDH levels, death rates, probability of 10-year survival rate and compared the causes of death for patients that received hydroxyurea and patients that received conventional treatment. The Laikon Study of Hydroxyurea in Sickle Cell Syndromes prospective (non-experimental correlational study) phase 2 study was done in the Thalassemia Center of Laikon General Hospital in Athens, Greece. The patients who had met the criteria including age greater than 16 years of age, greater than three painful sickle cell crises a year that required hospitalization or emergency room visits; the presence of jaundice at presentation or complications from sickle cell disease including stroke, acute chest syndrome during the last five years; WBC of $3 \times 10^9/L$ or greater, neutrophil count of $1.5 \times 10^9/L$ or greater and platelet count of $100 \times 10^9/L$ or greater. If at any point the patients that were receiving conventional treatment met these criteria, they were then allowed to start taking the hydroxyurea. There were 330

participants with age ranging from 20 to 76 years old with median age being 42 years old, 136 being men and 194 being women. One hundred and thirty-one had severe disease and were treated with hydroxyurea while 199 patients received conventional treatment including analgesics, hydration and oxygen.

These results were interpreted by multiple different tests including: Mann-Whitney U test, nonparametric Kolmogorov-Smirnov test, Wilcoxon nonparametric test, nonparametric Fiedman and Wilcoxon tests, McNemar test, Spearman nonparametric correlation test, Kaplan-Meier method, Fisher exact test and Cox proportional hazards regression analysis. There was a reduction in severe painful crises with 7.34 +/- 6.5 episodes a year before hydroxyurea to 0.025 +/- 0.026 episodes per year after taking hydroxyurea, P value = <0.001. There was a significant reduction of transfusion requirements with 1.5 +/- 5/9 per year before hydroxyurea treatment to almost zero during treatment, P value = < 0.001. There was a significant decrease in hospital admissions from 2.11 +/- 2.96 per year before treatment to 0.041 +/- 0.081 per year after hydroxyurea, P value = < 0.001. There was also a significant decrease in the incidence of chest syndrome from 6.1% prior to treatment to 0.8% after treatment, P value = 0.016. \

Patients taking hydroxyurea had a significant increase in total Hb and HbF and significant reduction in leukocytes, platelets reticulocytes, serum bilirubin and LDH levels. Compared to the patients who had conventional therapy, they had a statistical significant reduction in Hb and platelet counts but did not have any statistical significant changes in reticulocytes, serum bilirubin and LDH levels. The death rate for patients who received hydroxyurea was 9.9% while the death rate for patients who did not receive hydroxyurea was 24.6%, P value = 0.001. The probability of a 10-year survival rate for patients that were taking the medication was 86%, patients that did not take the medication was 65%, P value = 0.001.

The patients that did not receive hydroxyurea had more deaths caused by strokes, vasoocclusive crises, liver dysfunction and pulmonary hypertension. This study is considered to be a level III due to it being a prospective (non-experimental correlational) study, has a quality of 5 and because the results show moderate evidence to support the effectiveness of hydroxyurea, its strength is a B.

SYNTHESIS

Based on the review of these five research studies, there are several conclusions that can be drawn. The main conclusion is all the studies were related to the variables of interest finding that hydroxyurea has beneficial results for adult patients that have severe sickle cell disease with minimal risks (Ballas et al., 2010; Ferguson et al., 2002; Smith et al., 2011; Steinberg et al., 2003; Voskaridou et al., 2010). As stated previously, Smith et al. (2001), Steinberg et al. (2003), and Voskaridou et al. (2010) had statistically significant results that demonstrated decreased mortality rate with patients that took hydroxyurea while Steinberg et al. (2003) and Voskaridou et al. (2010) had statistically significant results for decreased painful crises, analgesic use, hospitalizations and higher levels of HgF with patients that took hydroxyurea. Ballas et al. (2010) revealed that their research showed decreased use and amount of analgesia at home, acute care visits and inpatient visits but some of their data was not statistically significant. However, their data revealed a decrease in the amount of inpatient painful crises and acute care visits that was significantly significant. Ferguson et al. (2002) demonstrated their research showed a decrease in the number of transfusions and hospital admissions but their P values were not evaluated as statistically significant.

The samples of all the studies were well represented with a diverse population. Overall, they had strong methodology incorporating large sample sizes, a variety of designs and evaluation tools and included samples that adequately represented the target population. All the

studies had patients with severe sickle cell anemia take the hydroxyurea while the ones with a mild form of the disease would not take hydroxyurea or have conventional treatment (Ballas et al., 2010; Ferguson et al., 2002; Smith et al., 2011; Steinberg et al., 2003; Voskaridou et al., 2010). Because their research showed there was minimal risk to taking hydroxyurea with many benefits, this created a low risk and high benefit ratio making the studies safe.

These studies greatly impact clinical practice. Ballas et al. (2010), Smith et al. (2011) and Voskaridou et al. (2010) explain that hydroxyurea is the only medication currently on the market that can help slow down or prevent complications due to sickle cell disease. The use of hydroxyurea is also considered a national guideline for treating sickle cell disease but it is still underutilized (Brawley, 2008). Providers should apply this knowledge to their practice, be advocates for their patients and provide appropriate information regarding hydroxyurea and confidently prescribe this medication.

Overall, these studies have demonstrated beneficial results to adult patients that are diagnosed with severe sickle cell disease when taking hydroxyurea (Ballas et al., 2010; Ferguson et al., 2002; Smith et al., 2011; Steinberg et al., 2003; Voskaridou et al., 2010). Some of the studies have shown higher statistical significance than others but they all share some type of advantage to utilizing this medication. This finding is very pertinent to this critical appraisal as it was the main variable of interest. There does not appear to be any overall methodological issues that could account for inconsistencies or lack of significant finding. The only study that did not have significant statistics was from Ferguson et al. (2002). This may have been due to a small sample size and could lead to a decrease in statistical significance.

RECOMMENDATIONS

Administering hydroxyurea for the treatment of sickle cell disease is novel in the minds of medical providers and patients with sickle cell disease. Based on this literature review,

hydroxyurea has been found to be highly beneficial at reducing morbidity and mortality in adults with severe sickle cell anemia (Ballas et al., 2010; Ferguson et al., 2002; Smith et al., 2011; Steinberg et al., 2003; Voskaridou et al., 2010). It is the responsibility of the advanced practice nurse to fully utilize this evidence in caring for their patients.

Many patients with sickle cell disease are part of an underserved population and may not receive proper health care due to a multitude of factors. Factors may include lack of education, money and resources. Properly educating patients with sickle cell disease about this medication and all treatment options is essential for the patients to make well-educated, safe decisions, leading to improved health care outcomes.

SUMMARY

Due to the innovative nature of this topic, there are several recommendations for further research. The first is hydroxyurea should be researched in patients with every degree of sickle cell disease to evaluate the benefits of this medication. This allows the medication to be better developed and employed in a larger population of sickle cell patients. Research should also be done on the perceptions and barriers patients with sickle cell disease have regarding treatments. Based on these results, providers can better educate their patients and create an individualized plan of care that is appropriate for each patient.

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