Effectiveness of Hydroxyurea and Blood Transfusions to Treat Sickle Cell Disease

Thousand Oaks High School

AP Research

April 2019

Word Count: 4300

Abstract

Sickle cell disease is a hereditary disease that has a series of problems, the most common one being pain episodes. Currently the two most common treatments for sickle cell disease is hydroxyurea and blood transfusions. Both treatments have negative effects but none of those effects are important enough to stop the use of the treatments. There has also not been an actual statistical comparison between the two treatments, so it is unknown which one is more effective than the other. This paper analyses the two different treatments and focuses on three different factors of the disease, the amount of acute chest syndrome evens, painful crisis events, and infections. All three symptoms lower the quality of life of the SCD carrier by interfering with their everyday tasks and forces them to live in a specific way in order to reduce the amounts of negative events.

Introduction

Sickle cell disease (SCD) occurs in approximately 80,000 people in the United States each year (Centers for Disease Control and Prevention, 2017). In African American births, it is seen in about one out of every 365 newborns and in Hispanic Americans, it is seen in about every one in 16,300 newborns. As seen in Figure 1, SCD cases in Africa account for nearly 70% of all cases worldwide with the reason being that Africa has a long history of malaria, a disease that causes red blood cells to be infected by the Plasmodium parasite. Plasmodium is a type of parasite that attacks and spread through red blood cells. Despite the abnormality of SCD, individuals with the sickle cell trait have become resistant to the effects of malaria (Williams et al., 2005). Even though the sickle gene may protect people from malaria, it leaves them vulnerable to other infections creating even more problems. In areas such as the United States, Malaria is not a recurring problem, so over time, the rate of SCD among African Americans has gone down. Africa has the highest amount of SCD cases, but it also has the lowest childhood SCD survival rates compared to the rest of the world, meaning that there is a significant amount of people dying (Figure 2). SCD disproportionately affects Africans and since they have the lowest survival rates, many of those people require help.

SCD is a group of hereditary red blood cell disorders caused by the sickle shaped cells (Figure 3) which form due to problems with hemoglobin, a protein that helps carry oxygen in red blood cells through the bloodstream. The hemoglobin protein is made up of two different subunits of proteins: beta-globins (β-globin) and alpha-globins (α-globin). When the hemoglobin in a red blood cell arrange into long and parallel fibres, stretching out the cell, it is known as polymerization, which is the cause of SCD (U.S. National Library of Medicine,

2018). The polymerization is the result of a point mutation with the β-globin chain of hemoglobin, located on the short arm of the 11th chromosome. The glutamic acid, a hydrophilic amino acid located in the sixth position of the β-globin chain is replaced with the hydrophobic amino acid valine. During polymerization, the fibres are created from interactions between the newly added valine and the hydrophobic regions. After the change, the two α-globin subunits merge with two mutated β-globin subunits creating the sickle hemoglobin or HbS, the hemoglobin which causes SCD. When the body has low oxygen, there will be a missing polar amino acid in the sixth position of the β-globin chain. As a result, the hemoglobin polymerizes and starts connecting together into long rods in a red blood cell (U.S. National Library of Medicine, 2018). As seen in Figure 4, the normal red blood cell has normal hemoglobin spread throughout the cell and not connected, while the sickle cell has long and connected hemoglobin, stretching out the cell. The long rods cause the cells become distorted and sickle-shaped, causing problems such as anemia, pain due to blocked blood vessels, acute chest syndrome, vaso occlusive crisis, an increase in infections, swelling of hands and feet, and in some cases, vision problems (Ballas et al., 2012). Acute chest syndrome causes coughing and shortness of breath and if left untreated, can be fatal. There are multiple factors that can cause acute chest syndrome, including blocked blood vessels around chest area, asthma, pneumonia, and pulmonary embolism. Vaso occlusive crisis, the most common reason individuals with SCD seek professional help since it causes episodes of acute pain and is the more frequent symptom of SCD. (Ballas et al., 2012)

Anemia as a result of SCD occurs when the fragile sickle cells break and die, leaving the body without enough red blood cells. Normal red blood cells typically live for

approximately 120 days before needing to be replaced; however, sickle cells usually die within 10 to 20 days, leaving a shortage of red blood cells. When there are not enough red blood cells, the muscles in the body are not able to receive the oxygen it needs become energized, causing fatigue (Parise, 2016). Sickle cells can damage organs that fight infections, such as the spleen, due to a lack of oxygen and red blood cells, thus, leaving the body more vulnerable to infections.

SCD can be especially dangerous in infants and children since they are more prone to infections than adults. As a result, doctors commonly give younger patients antibiotics or vaccinations to prevent possible life-threatening infections, such as pneumonia (Chakravorty, 2014). Younger individuals with SCD will find themselves with delayed growth, since the red blood cells that provide their body with the oxygen and nutrients are crucial for growth (Ballas et al., 2012). Typically, infants and children with less healthy red blood cells will be farther behind in overall growth when compared to their peers, and teenagers will have a delay in puberty (Platt et al., 1991). Blockage in blood vessels is a result of the abnormal shape of the sickle cells, leading to pain in areas where there is an absence of blood. Pain from SCD can occur almost anywhere in the body in multiple areas at one time. It occurs mostly in the abdomen, arms, chest, lower back, and legs. In addition to affecting people physically, SCD can also affect them mentally (McClish et al., 2005). For example, it can cause people to feel sad or frustrated. Furthermore, the limitations caused by the disease can impose negative effects on a person's daily life, potentially making them feel isolated from others and even cause depression.

Sickle Cell Trait

About one to three million of Americans are affected by the sickle cell trait(SCT) and 10 percent of all African Americans have it. People with the SCT were born with only one allele of the sickle hemoglobin and one for the normal hemoglobin. However, people with SCD have two of the sickle cell allele. If only one parent has SCT and the other was normal, then their children will either have a 50% chance of having SCT or 50% chance of not having it. But if both parents have SCT, then there is a 25% chance that their children will have SCT, 25% chance that their children will have SCD, and 25% chance that their children will be normal (Centers for Disease Control and Prevention, 2017).

Environmental Factors

SCD is most common in areas where Malaria is or was a major problem, due to how the cells are like. Since sickle cell do not live for a long time, the body disposes of them by sending them to the spleen, and as a result, the parasite causing Malaria is destroyed. Due to the abnormal shape of sickle cells and the membrine being weak and inflexible, the nutrients inside of the cells leave and are lost. Leaving the Plasmodium parasite with not enough nutrients to survive so it will eventually die (Williams et al., 2005).

There are a series of factors that contribute to the rate of polymerization of HbS, such as temperature, hypoxia, and if the RBC has enough water. All three can be changed depending on certain environmental factors. In Africa, the conditions of SCD is much more severe than in other areas of the world, most likely due to the hot climate, poor medical care, and higher likelihood of getting infectious diseases. Both extremely hot and cold climates can

cause problems with in people with SCD. For example, a common occurrence among SCD patients is acute pain when exposed to cold temperatures (Tewari, Brousse, Piel, Menzel, Rees, 2015).

Two Main Treatments

Hydroxyurea.

Currently, hydroxyurea, an oral medicine (Figure 5) taken daily to prevent the adverse effects of SCD, is the main drug used as a treatment for SCD. Hydroxyurea increases the amount of fetal hemoglobin (HbF) in the blood, providing protection against HbS, since it inhibits the HbS polymerization (Brawley et al., 2008). Newborn babies have more HbF than adults, which is why they typically see little to no adverse effects from SCD early on. HbF usually stops being produced in infants after six months, but because the HBF production ends at varying times depending on the circumstances of the infant, the switch from fetal to adult hemoglobin is unknown (Edoh, Antwi-Bosaiko, & Amuzu, 2006). Hydroxyurea works by first increasing HbF production, leading to a decrease in sickle cell production. As a result, there is a decrease in red blood cell membrane damage, hemolysis, and inflammation. All of which lead to an improved tissue oxygenation throughout the whole body (Agrawal, Patel, Shah, Nainiwal, & Trivedi, 2013). The recommended dosage for adults is 20 to 30 mg/kg daily and for adolescents is 10 to 20 mg/kg daily.

Blood transfusion.

Another method used to treat SCD is blood transfusions which increases the amount of normal red blood cells, because they can live longer in the circulatory system and have a

larger surface area than red blood cells with sickle hemoglobin. Blood transfusions also decrease the risk of clogged blood vessels thus improving oxygen delivery throughout the body. Blood transfusions are the most common non-drug treatment for SCD and has been used for many years in patients. The reason why it is effective treatment method is because when blood containing normal hemoglobin from a healthy host is transfused into a SCD patient, it compensates and reverses the negative effects of HbS.

There are two types of transfusions: a simple or top-up transfusion and exchange blood transfusion. Top-up transfusions requires a few units of blood that is usually given through a drip, a small tube that is placed in the vein of the body (Marouf, 2011). This type of transfusion is meant to replace blood that has been lost. An exchange blood transfusion is the type of transfusion that is mainly used for SCD. It replaces blood containing HbS with blood containing normal hemoglobin. It is usually done through an automated specialized equipment and the reason for that is so a precise amount of sickle blood from the patient can be removed and normal blood can be added as a replacement (Swerdlow, 2006). Saline, a solution with a 0.9% concentration of sodium chloride is added alongside the normal blood, since the concentration of sodium chloride in blood is similar to the concentration in saline (Marouf, 2011). The reason why saline is added is to increase the intravascular and the interstitial volume, decreasing the osmotic pressure since the blood is being dilute.

If an exchange blood transfusion is done within 48 hours of diagnosis for ACS in a SCD patient, then the problems will most likely stop. However, simple transfusions have also been used to improve the symptoms of ACS, if used within 24 hours of diagnosis (Swerdlow, 2006). There are three reasons why patients with SCD are given transfusions. The first one is

to increase the amount of oxygen red blood cells can carry, allowing the body to receive enough oxygen for it to function properly. The second being to decrease blood viscosity, the thickness of the blood, which is typically higher in SCD individuals The third reason is to lower the amounts of red blood cells being turned into sickle cells.

Adverse effects.

Hydroxyurea and blood transfusions are two different treatments that have both been clinically tested thoroughly and have made great impacts to sickle cell disease patients. However, there has been constant debate about the potential and unknown risks of hydroxyurea, since it has been approved by the FDA, such as the unknown toxicities that could result from long term use (Brandow & Panepinto, 2010). A common side effect of hydroxyurea is cytopenia, when antibodies destroy mature red blood cells reducing the number of red blood cells in the bloodstream, thus countering the purpose of taking the drug in the first place (Brandow, & Panepinto., 2010). Blood transfusions also have adverse effects, such as alloimmunization and acute or delayed hemolytic transfusion reaction. Alloimmunization occurs when immunocompetent patients receive transfusions have an immune response to the antigens from the blood which came from another host. As a result, there can be consequences with the blood due to the specific antigens that are involved, such as clotting (Yazdanbakhsh, Ware, & Noizat-Pirenne, 2012). Examining the benefits surrounding each treatment and the overall effectiveness of each treatments will allow a deeper understanding of which one is more beneficial for wellbeing of SCD patients.

Purpose

The purpose of this research paper is to investigate the effectiveness of the two most common treatments for sickle cell disease, blood transfusions and hydroxyurea. Both treatments have adverse effects which, overall, do not outweighed the benefits of the treatments, since they are being widely used for SCD. However, there has not been any studies directly comparing the two, so there is no exact answer on which treatment is better. One reason why there has not been studies directly comparing their effectiveness because of how different the two treatments are, there could possible be a lack of comparable data. However, if one treatment is shown to be more effective than the other due to the benefits or adverse effects, then it should be prefered over the other.

Research Question

What is the effectiveness of hydroxyurea and blood transfusions as a treatment for sickle cell disease?

Alternative Hypothesis

Blood transfusion is more effective than hydroxyurea in treating sickle cell disease due to the unknown toxicity of hydroxyurea.

Null Hypothesis

There is no significant overall difference between the effectiveness of blood transfusion and hydroxyurea to treat SCD.

Methods

Data Sources

The design of this paper is that of a systematic literature review. Research databases including Google Scholar, PUBMED-NCBI, ResearchGate, ScienceDirect, Blood Journal, PLOS, BioMed Central, etc. were used to gather studies analyzing the effectiveness of hydroxyurea and blood transfusions as treatments for sickle cell disease. Keywords, such as "sickle cell disease," "hydroxyurea treatment," "blood transfusions," etc. were used to collect informative articles. Additional information was gathered from the references of used articles.

The time range for the data used is from 1998 to 2019 since hydroxyurea was approved by the FDA as a treatment for SCD in 1998. Since then, there have been studies that focused specifically on the effects of Hydroxyurea on SCD, however, some studies did not focus on the data needed to compare it with blood transfusion. Subsequently, the articles collected on Hydroxyurea were narrowed down, which limited the data that was available. Articles used in the paper that are older than 1998 were not used for data collection, and were instead used for background information. The year range for each experiment was within one to nine years to keep the time consistent. The gender of the patients were not taken into consideration when narrowing the data because SCD does not have sex predilection due to SCD not being an X-linked disease.

Using a systematic literature review was the most effective method for this specific study because conducting experiments would not be needed to gather data as both treatments already have a significant amount of literature to support their respective costs and benefits. It also would not be possible to conduct such experiments due to the constraints of a high school setting. Other methods such as using secondary data or surveys are not appropriate either. Secondary data would not provide enough information to complete the data collection and surveys do not provide the same type of data that is needed.

Data Extraction

After all the papers on hydroxyurea or blood transfusions were collected, some of the papers were removed if they did not include at least two of the events in patients that were going to be used. The three events chosen were acute chest syndrome, vaso occlusive crisis or pain crisis, and infections. Most of the papers included acute chest syndrome and pain crisis, but more than a few did not include infections. The three events were chosen because they were the most commonly included events in the studies, however, there were more specific reasons. Acute chest syndrome was chosen because it is the most common cause of death in SCD patients and vaso occlusive is the most common symptom in SCD patients. An effect of hydroxyurea is that it can lower the amount of white blood cells in a patient and it also can lower the amount of platelets, which is required for blood clotting, and as a result, the chance of infections is increased temporarily. Infections from blood transfusions are also possible from HIV, however, none of the studies used had such occurrences. Other ways of infections that can come from blood transfusions are accidental exposures to factors such as viruses,

bacteria, parasites, and prions while transmitting blood.Data on infections was chosen because there was a noticable difference between the data seen in the two treatments.

Data and Statistical Analysis

The data collected from the studies were first recorded in Google Sheets for convenience, then transferred to Excel. Since Google Sheets does not offer the statistical analysis that Excel has, all the data was analyzed in Excel. From Excel, The averages of the data were created and three two-tailed tests were conducted on the three different events, comparing those of blood transfusions to those of hydroxyurea. At first there was a complication regarding the amount of patients being different for each study causing the data to be not comparable. This problem was fixed by dividing the amount of events to the corresponding amount of patients in order to find the percentage of events for group of patients. The t-test was done of the percentage values not the number of events.

Results

Table 1. The amount of events of acute chest syndrome, painful crisis, and infections that occurred in a set amount of patients that received blood transfusions as a treatment for SCD. The average of the patients and events are given.

	Number of Patients	Acute chest syndrome	Painful Crisis	Infection
Alvarez, O. (2013)	**66**	**4**	**62**	**3**
DeBaun, M. R. (2014)	**99**	**5**	**96**	**1**

Miller, S. T. (2001)	**59**	**2**	**9**	**-**
Miller, S. T. (2001)	**63**	**4**	**17**	**-**
Vichinsky, E. P. (2000)	**264**	**16**	**47**	**3**
Wang, W. C. (STOP 1998) (2013)	**63**	**4**	**11**	**0**
Ware, R. E. (2016)	**61**	**3**	**23**	**4**
Average	**96**	**5.4**	**37.9**	**2.2**

Table 2. The amount of events of acute chest syndrome, painful crisis, and infections that occurred in a set amount of patients that received hydroxyurea as a treatment for SCD. The average of the patients and events are given.

	Number of Patients	**Acute Chest Syndrome**	**Painful Crisis**	**Infections**
Alvarez, O. (2013)	**67**	**9**	**38**	**9**
Gulbis, B. (2005)	**32**	**3**	**22**	**0**
Gulbis, B. (2005)	**92**	**3**	**31**	**0**
Jain, D. L. (2012)	**30**	**0**	**18**	**10**

Kinney T. R. (1999)	**84**	**10**	**76**	**23**
Koren, A. (1999)	**60**	**7**	**39**	**-**
Wang, W. C. (2013)	**96**	**8**	**63**	**0**
Ware, R. E. (2016)	**60**	**5**	**11**	**4**
Average	**65.1**	**5.6**	**37.3**	**7.6**

Table 3. Rate of the three different events to the corresponding groups of patients for the data from table 1.

	Acute chest syndrome	**Painful Crisis**	**Infections**
Alvarez, O. (2013)	**0.06**	**0.93**	**0.05**
DeBaun, M. R. (2014)	**0.05**	**0.96**	**0.01**
Miller, S. T. (2001)	**0.08**	**0.15**	**-**
Miller, S. T. (2001)	**0.06**	**0.27**	**-**
Vichinsky, E. P. (2000)	**0.06**	**0.17**	**0.01**
Wang, W. C. (STOP 1998) (2013)	**0.06**	**0.17**	**0**
Ware, R. E. (2016)	**0.05**	**0.37**	**0.07**

Average	**0.06**	**0.43**	**0.03**

Table 4. Rate of the three different events to the corresponding groups of patients for the data from table 2.

	Acute Chest Syndrome	**Painful Crisis**	**Infections**
Alvarez, O. (2013)	**0.13**	**0.57**	**0.13**
Gulbis, B. (2005)	**0.09**	**0.69**	**0**
Gulbis, B. (2005)	**0.03**	**0.34**	**0**
Jain, D. L. (2012)	**0.03**	**0.34**	**0**
Kinney T. R. (1999)	**0**	**0.6**	**0.3**
Koren, A. (1999)	**0.12**	**0.9**	**0.27**
Wang, W. C. (2013)	**0.12**	**0.65**	**-**
Ware, R. E. (2016)	**0.08**	**0.66**	**0**
Average	**.08**	**0.57**	**0.11**

Table 5. The p-values from the t-tests done on the percentages of three different events(acute chest syndrome, painful crisis, and infections) comparing hydroxyurea with blood transfusions.

	Acute Chest Syndrome	**Painful Crisis**	**Infections**

P-value	**0.24**	**0.39**	**0.16**

Summary of Results

The numbers in Table 3 and Table 4 represent the rate of occurrence of each event in the corresponding group of patients in the studies. The data that was collected from the different papers shows that both hydroxyurea and blood transfusions are effective at lowering the rate at which symptoms of SCD occured. Some of the studies also included a placebo alongside the actual treatment, but it was not necessary to include the results of the placebos since it was already known that both treatments are effective. However, if one of the studies had proven a method to be ineffective, then the data on placebos would be included, but none did.

Table 1 and 2. The data contained in the two tables were taken from studies that were taken from papers which conducted experiments on the effectiveness of either blood transfusions or hydroxyurea as treatments for SCD. The number of patients for each of the studies included were different, so just comparing the amount of events between the two treatments would be inaccurate. Some studies did not include the amount of infections per group of patients that received a treatment.

Table 3 and 4. Since the data from Tables 1 and Table 2 could not be compared directly, the rate of events per group of patients was found. The averages of occurrences for acute chest syndrome were similar between the two treatments, with hydroxyurea being

greater by .02. The average rate of occurrence of painful crisis for hydroxyurea was greater by about .14 and for infections, for hydroxyurea, the value was greater by .08.

Table 5. The p-values were rounded to the nearest hundredths place. Using the rates from Table 3 and Table 4, there two-tailed tests were conducted based on the data on the three events, with the p-value of acute chest syndrome being 0.24, painful crisis being 0.39, and infections being 0.16.

Discussion

When comparing the results of the three different events of SCD, both infections and painful crisis saw greater differences in the rate of occurrences than acute chest syndrome when compared between hydroxyurea and blood transfusion. All three of the average percentages of the events were greater for hydroxyurea, meaning that there was a higher rate of symptoms among the patients who used hydroxyurea than those who had blood transfusions.

Patients that received hydroxyurea as their treatment saw a higher chance of having an infection. It is much harder to prevent infections while using hydroxyurea than it is when using blood transfusions. The reason why patients who had blood transfusions had lower chances of getting infections is because blood transfusions for the patients are done in sterile environments with sterile tools. However, this does not necessarily mean that infections will be completely prevented as there were some rare cases when infections occurred.

For acute chest syndrome, there was no significant differences in the number of events that occured between the two treatments most likely because both hydroxyurea and blood transfusion improve the flow of blood in the blood vessels, decreasing the amount of blockages that come from sickle cell. Meaning that it is less likely for the chest area to be affected by SCD.

The p-value for acute chest syndrome comparing hydroxyurea with blood transfusions was 0.24 and the p-value for painful crisis was 0.39. The p-value for infections was 0.16 which is lower than both of the other two, however, all three values are greater than .05 meaning that the alternative hypothesis is rejected and the null hypothesis is accepted. Through analysis of the three factors, acute chest syndrome, pain crisis, and infections, the p-values reflect that there is no significant difference in effectiveness between blood transfusions and hydroxyurea when treating SCD.

After using the two-tailed test on the data, the p-values that were came out of it were higher than expected. Since the averages of the three events from Table 4 were all greater than the events from Table 3, it was expected than the p-values would be smaller, indicating that blood transfusions are more effective. This was not what was found however. The p-values calculated show that there was no significant difference between the two treatments, but the numbers show another result, this may be due to sources of error regarding the use of the percentage of events per sample group since it would not have been accurate to compare data from different studies that had different amount of patients tested.

Conclusion

The systematic literature review conducted on evaluating the effectiveness of hydroxyurea and blood transfusions as treatments for SCD shows that the alternative hypothesis should be rejected and that the null hypothesis should be accepted. Both treatments are currently being used widely for SCD patients and although their effects on acute chest syndrome and vaso occlusive crisis are similar, hydroxyurea has shown to have higher rates of infections among the patients. There are precautions before receiving a blood transfusions which can help lower the chance of an infection, however, it is much harder to lower the risk of infections from hydroxyurea since the amount of white blood cells and platelets are being lowered. A temporary decrease in platelets can also lead to anemia and an increase in bleeding, both of which are not seen in blood transfusions.

Although quantitatively, the data suggests that there is not a significant difference between the treatments, qualitatively, there is a difference. This discrepancy may be a result the studies examined did not properly cover infections the same way. Since infections can be side effects of both hydroxyurea and blood transfusions, the studies examined included included data on it, however, the cause of infections are different for both treatments. With infections in blood transfusions being preventable using different sterilization methods, but the infections caused by hydroxyurea can not be prevented as easily.

Further Work

To further contribute to this study, more studies could be conducted on similar areas between the two different treatments. For example, the studies used to compare the effectiveness of hydroxyurea and blood transfusions on SCD did not study similar characteristics to determine effectiveness, so there was not a lot of information that could be use to directly compare the two. Although, the data available was significant enough to make a feasible comparison, if there were more similar comparative studies then the results of this paper/study/review would hold even more significance.

As of right now, there is no cure that is widely available for SCD patients. However, new studies have been tested regarding the use of blood stem cells or bone marrow transplants in order to cure SCD completely. Although the bone marrow transplants have been deemed too toxic for adults, it has been used successfully on most children tested, though he number of children who were tested is not high (Bernaudin et al., 2007). The process starts by giving the patient high doses of chemotherapy and destroying all of the child's bone marrow. After all the marrow is gone, it is replaced by a donors bone marrow, typically a healthy sibling. Since the patient's body might reject the transplanted marrow, most of them need to take immunosuppressants for a couple of months with some taking them for a few years (National Institues of Health, 2016). Even though research on the treatments is important and relevant to the current conditions of SCD, it needs to be made more widely available in developing areas, such as Africa. Due to Africans being disproportionately affected by SCD compared to the rest of the world and their survival rates are oppositely disproportionate.

Figures

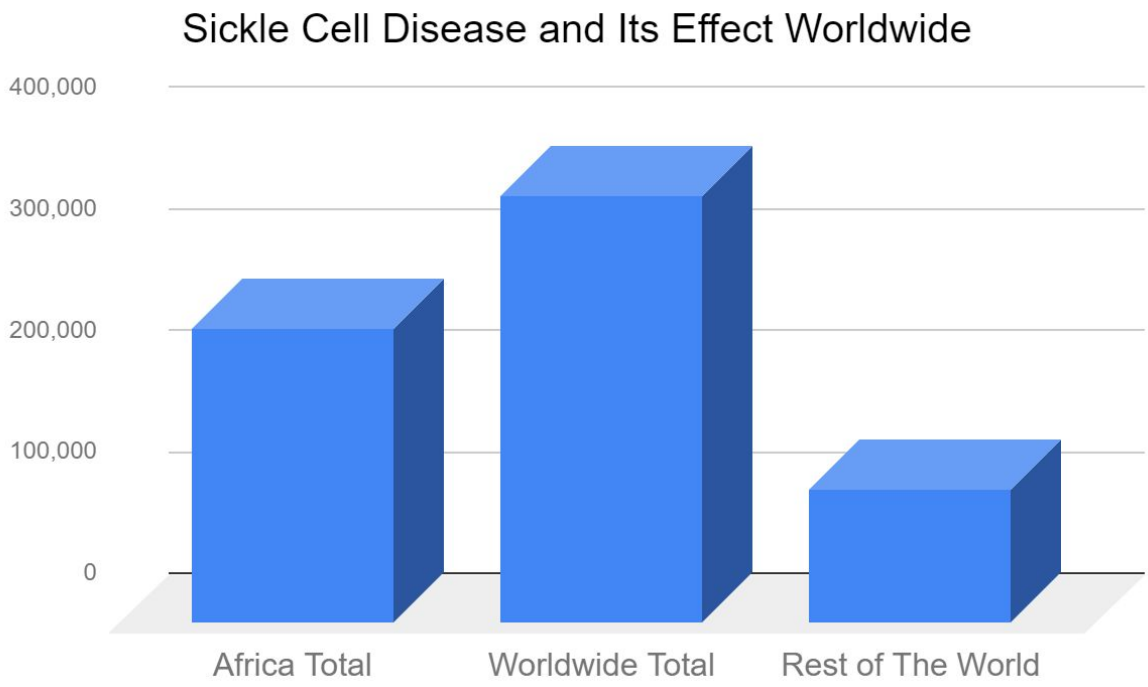

Figure 1. The amount of people affected by SCD in Africa and the rest of the world, which is excluding Africa. The graph shows how there is a significantly greater amount of cases in Africa then the rest of the world. Data retrieved from National Institutes of Health and Centers for Disease Control and Prevention.

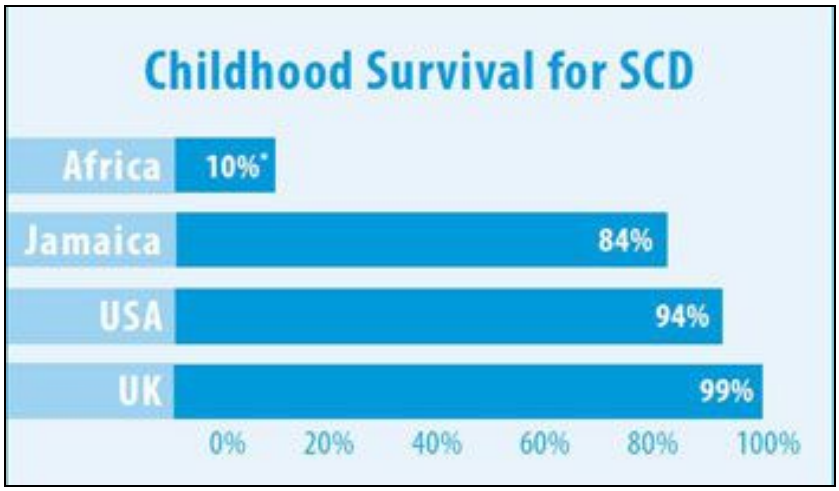

Figure 2. The graph shows the survival rates among children in different areas of the world and Africa's survival rates are low due to the overwhelming amount of people who have the disease and the poor living and medical conditions. Graph acquired from National Institutes of Health.

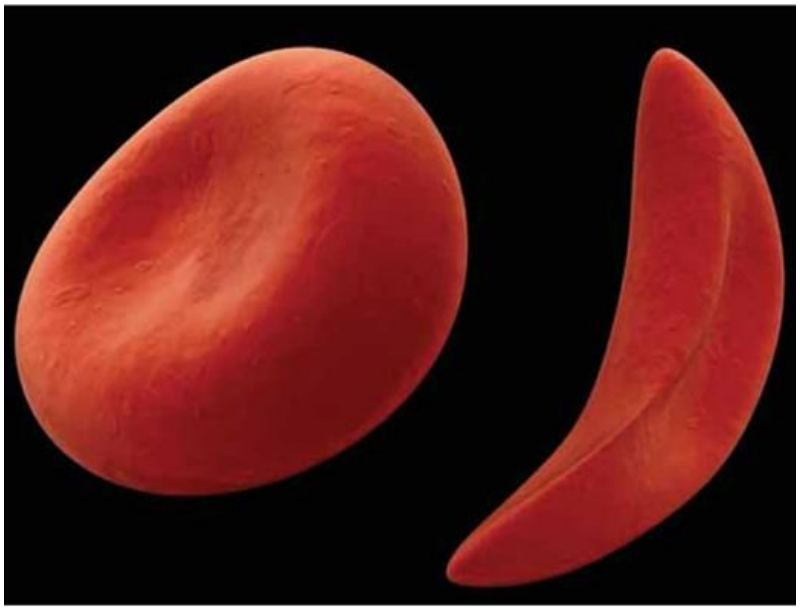

Figure 3. On the left is a normal red blood cell and on the right is a sickle-shaped red blood cell (Harley, 2013). The normal red blood cells have more surface area than the sickle shaped cells, so they are able to carry more oxygen throughout the body. Sickle Cells are less flexible and break much easier than normal red blood cells.

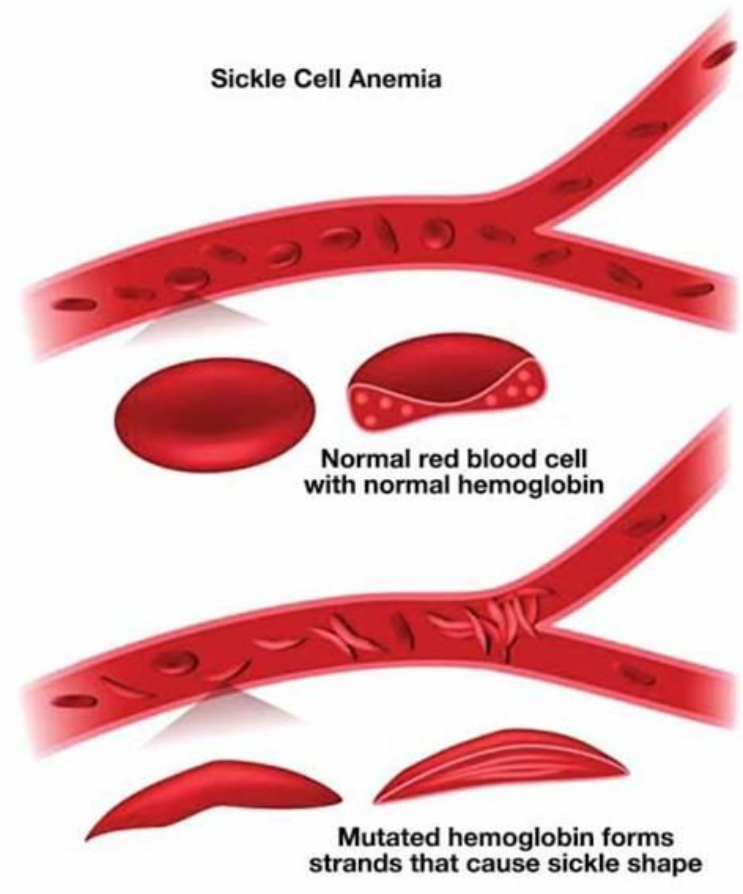

Figure 4. The blood vessel above shows normal red blood cells flowing through and below shows the sickle-shaped red blood cells blocking the blood vessels, stopping blood flow in certain areas of the body (below) (Harley, 2013). If there is a lack of blood in a certain area, then it will cause pain.

Figure 5. Oral hydroxyurea pill. The recommended dosage for adults is 20 to 30 mg/kg daily and for adolescents is 10 to 20 mg/kg daily. Retrieved from https://www.rxlist.com/hydrea-drug.htm

Acknowledgments

I would like to thank Dr. Nikki Malhotra for all her time spent helping me with my research during every part of my research process. Additionally, I would like to thank my expert advisors Dr. Gregory Kato for helping me most during the beginning of my project, narrowing down my research project, and also Dr. Martin Steinberg for his support throughout my research process and help with any questions about my topic. Lastly, I would like to thank Kea Turqueza for helping me with my research and giving me advice based off of her experience with AP research.

References

Agrawal, R. K., Patel, R. K., shah, V., Nainiwal, L., & Trivedi, B. (2013). Hydroxyurea in Sickle Cell Disease: Drug Review. Indian Journal of Hematology and Blood Transfusion, 30(2), 91–96. doi:10.1007/s12288-013-0261-4

Alvarez, O., Yovetich, N. A., Scott, J. P., Owen, W., Miller, S. T., … Schultz, W. (2013). Pain and other non-neurological adverse events in children with sickle cell anemia and previous stroke who received hydroxyurea and phlebotomy or chronic transfusions and chelation: Results from the SWiTCH clinical trial. American Journal of Hematology, 88(11), 932–938. doi:10.1002/ajh.23547

Ballas, S. K., Gupta, K., & Adams-Graves, P. (2012). Sickle cell pain: a critical reappraisal. *Blood*, 120(18), 3647–3656. doi:10.1182/blood-2012-04-383430

Bernaudin, F., Socie, G., Kuentz, M., Chevret, S., Duval, M., . . . Bertrand, Y. (2007). Long-term results of related myeloablative stem-cell transplantation to cure sickle cell disease. *Blood*, 110(7), 2749–2756. doi:10.1182/blood-2007-03-079665

Brandow, A. M., & Panepinto, J. A. (2010). Hydroxyurea use in sickle cell disease: the battle with low prescription rates, poor patient compliance and fears of toxicities. *Expert Review of Hematology*, 3(3), 255–260. doi:10.1586/ehm.10.22

Brawley, O. W. (2008). National Institutes of Health Consensus Development Conference Statement: Hydroxyurea Treatment for Sickle Cell Disease. *Annals of Internal Medicine*, 148(12), 932. doi:10.7326/0003-4819-148-12-200806170-00220

Data & Statistics on Sickle Cell Disease | CDC. (2017). Retrieved from https://www.cdc.gov/ncbddd/sicklecell/data.html

Chakravorty S, Williams TN (2015). Sickle cell disease: a neglected chronic disease of increasing global health importance. *Archives of Disease in Childhood*;100:48-53

DeBaun, M. R., Gordon, M., McKinstry, R. C., Noetzel, M. J., White, D. A., Sarnaik, S. A., … Casella, J. F. (2014). Controlled Trial of Transfusions for Silent Cerebral Infarcts in Sickle Cell Anemia. *New England Journal of Medicine*, 371(8), 699–710. doi:10.1056/nejmoa1401731

Discontinuing Prophylactic Transfusions Used to Prevent Stroke in Sickle Cell Disease. (2005). *New England Journal of Medicine*, 353(26), 2769–2778. doi:10.1056/nejmoa050460

Edoh, D., Antwi-Bosaiko, C., & Amuzu, D. (2006). Fetal hemoglobin during infancy and in sickle cell adults. African health sciences, 6(1), 51–54. doi:10.5555/afhs.2006.6.1.51

Gulbis, B. (2005). Hydroxyurea for sickle cell disease in children and for prevention of cerebrovascular events: the Belgian experience. Blood, 105(7), 2685–2690. doi:10.1182/blood-2004-07-2704

Harley, M. N. (2013). Current Treatments and Prospective Therapies to Manage Sickle Cell Disease. Laboratory Medicine, 44(4), e92–e96. doi:10.1309/lm383ucnpfohrjjy

Hydrea (Hydroxyurea): Side Effects, Interactions, Warning, Dosage & Uses. (n.d.). Retrieved from https://www.rxlist.com/hydrea-drug.htm

Jain, D. L., Sarathi, V., Desai, S., Bhatnagar, M., & Lodha, A. (2012). Low Fixed-Dose Hydroxyurea in Severely Affected Indian Children with Sickle Cell Disease. *Hemoglobin*, 36(4), 323–332. doi:10.3109/03630269.2012.697948

J Pediatr. (2001). Impact of chronic transfusion on incidence of pain and acute chest syndrome during the Stroke Prevention Trial (STOP) in sickle-cell anemia. *The Journal of Pediatrics*, 139(6):785-9. DOI: 10.1067/mpd.2001.119593

Kinney T. R., Helms R. W., O'Branski E. E., et al. Safety of hydroxyurea in children with sickle cell anemia: results of the HUG-KIDS study, a phase I/II trial. Pediatric Hydroxyurea Group. *Blood.* 1999;94 (5):1550–1554

Koren, A., Segal-Kupershmit, D., Zalman, L., Levin, C., Hana, M. A., Luder, A., & Attias, D. (1999). EFFECT OF HYDROXYUREA IN SICKLE CELL ANEMIA: A Clinical Trial in Children and Teenagers with Severe Sickle Cell Anemia and Sickle Cell beta-Thalassemia. Pediatric Hematology and Oncology, 16(3), 221–232. doi:10.1080/088800199277272

Marouf, R. (2011). Blood Transfusion in Sickle Cell Disease. Hemoglobin, 35(5-6), 495–502. doi:10.3109/03630269.2011.596984

McClish, D. K., Penberthy, L. T., Bovbjerg, V. E., Roberts, J. D., Aisiku, I. P., Levenson, J. L., … Smith, W. R. (2005). Health and Quality of Life Outcomes, 3(1), 50. doi:10.1186/1477-7525-3-50

Miller, S. T., Wright, E., Abboud, M., Berman, B., Files, B., Scher, C. D., … Adams, R. J. (2001). Impact of chronic transfusion on incidence of pain and acute chest syndrome during the Stroke Prevention Trial (STOP) in sickle-cell anemia. The Journal of Pediatrics, 139(6), 785–789. doi:10.1067/mpd.2001.119593

Parise, L. V., & Berliner, N. (2016). Sickle cell disease: challenges and progress. *Blood,* 127(7), 789–789. doi:10.1182/blood-2015-12-674606

Platt, O. S., Thorington, B. D., Brambilla, D. J., Milner, P. F., Rosse, W. F., Vichinsky, E., & Kinney, T. R. (1991). Pain in Sickle Cell Disease. New England Journal of Medicine, 325(1), 11–16. doi:10.1056/nejm199107043250103

Quan Li, Eric R. Henry, James Hofrichter, Jeffrey F. Smith, Troy Cellmer, Emily B. Dunkelberger, . . . William A. Eaton (2017). Kinetic assay shows that increasing red cell volume could be a treatment for sickle cell disease. *Proceedings of the National Academy of Sciences*, 201619054; DOI: 10.1073/pnas.1619054114

Research needed to treat sickle cell disease in Africa - Fogarty International Center @ NIH. (n.d.). Retrieved from https://www.fic.nih.gov/News/GlobalHealthMatters/november-december-2014/Pages/sickle-cell-disease.aspx#charts

Russell, M. R., Goldberg, H. I., Hodson, A., Kim, H. C., Halus J., Reivich M., and Schwartz E. (1984). Effect of Transfusion Therapy on Arteriographic Abnormalities and on Recurrence of Stroke in Sickle Cell Disease. *Blood.* 63(1):162-9.

Steinberg MH, Barton F, Castro O, et al. (2003). Effect of Hydroxyurea on Mortality and Morbidity in Adult Sickle Cell Anemia: Risks and Benefits Up to 9 Years of Treatment. *JAMA*. 289(13):1645–1651. doi:10.1001/jama.289.13.1645

Stem Cell Transplant Reverses Sickle Cell Disease in Adults. (2016, April 05). Retrieved from

https://www.nih.gov/news-events/nih-research-matters/stem-cell-transplant-reverses-sickle-cell-disease-adults

Swerdlow, P. S. (2006). Red Cell Exchange in Sickle Cell Disease. Hematology, 2006(1), 48–53. doi:10.1182/asheducation-2006.1.48

Tewari, S., Brousse, V., Piel, F. B., Menzel, S., & Rees, D. C. (2015). Environmental determinants of severity in sickle cell disease. Haematologica, 100(9), 1108–1116. doi:10.3324/haematol.2014.120030

Vichinsky, E. P., Neumayr, L. D., Earles, A. N., Williams, R., Lennette, E. T., Dean, D., . . . Manci, E. A. (2000). Causes and Outcomes of the Acute Chest Syndrome in Sickle Cell Disease. *New England Journal of Medicine*, 342(25), 1855–1865. doi:10.1056/nejm200006223422502

Wang, W. C., & Dwan, K. (2013). Blood transfusion for preventing primary and secondary stroke in people with sickle cell disease. The Cochrane database of systematic reviews, (11), CD003146. doi:10.1002/14651858.CD003146.pub2

Wang, W. C., Ware, R. E., Miller, S. T., Iyer, R. V., Casella, J. F., Minniti, C. P., . . . Thompson, B. W. (2011). Hydroxycarbamide in very young children with sickle-cell anaemia: a multicentre, randomised, controlled trial (BABY HUG). *BABY HUG investigators*, *377*(9778), 1663-72

Ware, R. E., Davis, B. R., Schultz, W. H., Brown, R. C., Aygun, B., Sarnaik, S., . . . Adams, R. J. (2016). Hydroxycarbamide versus chronic transfusion for maintenance of transcranial doppler flow velocities in children with sickle cell anaemia—TCD With Transfusions Changing to Hydroxyurea (TWiTCH): a multicentre, open-label, phase

3, non-inferiority trial. *The Lancet*, 387(10019), 661–670. doi:10.1016/s0140-6736(15)01041-7

Williams, T. N., Mwangi, T. W., Roberts, D. J., Alexander, N. D., Weatherall, D. J., Wambua, S., … Marsh, K. (2005). An Immune Basis for Malaria Protection by the Sickle Cell Trait. PLoS Medicine, 2(5), e128. doi:10.1371/journal.pmed.0020128

Yazdanbakhsh, K., Ware, R. E., & Noizat-Pirenne, F. (2012). Red blood cell alloimmunization in sickle cell disease: pathophysiology, risk factors, and transfusion management. *Blood*, 120(3), 528–537. doi:10.1182/blood-2011-11-327361