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The Role of Hydroxyurea-Induced Fetal Haemoglobin in Preventing Vaso-Occlusive Crisis in Sickle Cell Disease

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ABSTRACT

Background: Sickle cell disease (SCD) is a hereditary hemoglobin disorder, characterized by the presence of abnormal haemoglobin S. This abnormality leads to red cell deformation, chronic hemolysis and repeated vaso-occlusive crises (VOC). VOC is the leading cause of complications and hospital admissions in these patients. It occurs when small blood vessels become obstructed, leading to tissue ischemia and triggering inflammation. Hydroxyurea is currently one of the most effective drugs used to manage SCD. It exerts its therapeutic function by inducing the production of fetal haemoglobin (HbF). HbF inhibits polymerization of haemoglobin S, which prevents red blood cells from sickling and improves blood flow in the blood vessels.

Objectives: This study is to review the importance of using hydroxyurea as treatment for sickle cell disease. It reviews the role of hydroxyurea-induced fetal haemoglobin in preventing vaso-occlusive crises in sickle cell disease and examines the systematic function of fetal haemoglobin in reducing sickling, lowering white blood cell, reducing reticulocyte counts, reducing cells adhesion to vessel walls and improving the overall flow properties of blood in patients living with sickle cell disease.

Method: A thorough review of existing peer reviewed published literatures was conducted using Databases including PubMed, Scopus, and ScienceDirect were searched using the following keyswords; Hydroxyurea, Hydroxyurea-induced fetal haemoglobin, Vaso-occlusive, Sickle cell disease examining how hydroxyurea-induced fetal haemoglobin contribute in reducing sickling and vaso-occlusive complications in sickle cell disease.

Results: The findings of this review revealed that there are clinical benefits of hydroxyurea therapy in the management of sickle cell disease which include reduced frequency of painful crises, decreased hospitalization rates and improved quality of life in patients with sickle cell disease. Its ability to increase HbF levels plays an important role in preventing vaso-occlusive crises and improves outcomes for patients.

Conclusion: Hydroxyurea has clinical benefits in the management of sickle cell disease but limited by variability in patient response, potential bone marrow suppression and challenges related to monitoring, particularly in resource limited settings such as Nigeria. Its use requires careful laboratory monitoring due to potential myelosuppression and variability in patient response. Regular blood monitoring is therefore essential during treatment. Hydroxyurea remains a vital tool in managing sickle cell disease. These limitations necessitate the need for patient-specific dosing and ongoing healthcare system support to achieve the best possible treatment results.

KEYWORDS
Hydroxyurea, Hydroxyurea-induced fetal haemoglobin, Vaso-occlusive, Sickle cell disease.

1. Introduction

Sickle cell disease is a hereditary haemoglobinopathy, characterized by the inheritance of abnormal haemoglobin S (HbS), which results in chronic haemolytic anaemia, recurrent vaso-occlusive episodes and progressive multi-organ complications. The disorder arises from a single point

mutation in the βglobin gene (HBB), where the hydrophilic amino acid glutamic acid is replaced by the hydrophobic amino acid valine at the sixth position of the β-globin chain. Although this substitution involves only one amino acid residue, it profoundly alters the physicochemical properties of haemoglobin, leading to the formation of structurally abnormal haemoglobin S. Under conditions of deoxygenation, HbS molecules undergo polymerization, causing red blood cells to assume a characteristic sickle shape. These distorted cells exhibit reduced deformability, increased fragility and a shortened lifespan, resulting in chronic haemolysis and vascular obstruction. The resulting Vaso-occlusion and tissue ischemia are responsible for many of the acute and chronic complications associated with SCD, making it one of the most clinically significant inherited blood disorders worldwide. Sickle cell disease remains a significant global health burden, with its highest prevalence in subSaharan Africa, particularly Nigeria, where it contributes substantially to morbidity and mortality among children and young adults (5). Its clinical impact extends beyond anaemia, as it affects multiple organs and systems and severely reduces quality of Vaso-occlusive crisis is one of the most clinically significant complications of SCD. It occurs when sickled red blood cells, along with activated endothelial cells and inflammatory mediators, block small blood vessels. The result is impaired blood flow, tissue hypoxia and severe pain. Recent evidence shows that vaso-occlusive crisis is not only caused by blocked blood vessels but also by inflammation that continues and worsens the process (3 & 4). Fetal haemoglobin plays a protective role in SCD by inhibiting the polymerisation of HbS within red blood cells. Higher HbF levels help to reduce sickling and vaso-occlusive crises, making HbF an important modifier in disease severity. Hydroxyurea is currently the most widely used disease-modifying agent in SCD. It functions by inducing HbF production, which reduces HbS polymerisation and helps maintain red cell deformability. In addition, it reduces leukocyte counts and decreases cellular adhesion, all of which given these established effects, hydroxyurea remains highly relevant in modern sickle cell management. Understanding how hydroxyurea-induced fetal haemoglobin prevents vaso-occlusive crisis is therefore essential for improving clinical outcomes and guiding effective patient

2. Pathophysiology of Sickle Cell Disease

Sickle cell disease (SCD) is an inherited haemoglobin disorder resulting from a mutation in the βglobin gene, leading to the substitution of valine for glutamic acid at the sixth codon position. This structural alteration produces haemoglobin S (HbS), which has abnormal physical and chemical properties compared to normal adult haemoglobin (HbA). The disease is inherited in an autosomal recessive pattern, with homozygous HbSS presenting as the most clinically severe form (9). Sickle cell disease is initiated by the polymerization of HbS in its deoxygenated form. Under conditions of hypoxia, acidosis, dehydration, or infection, HbS molecules aggregate into long, rigid polymers that distort red blood cells into the characteristic sickle shape. These sickled erythrocytes exhibit reduced deformability, increased rigidity and shortened survival, leading to chronic hemolytic anaemia (11). Repeated episodes of sickling and reversal cause permanent damage to the membrane and disrupt normal red cell dynamics. These abnormalities increase blood viscosity and impair blood flow through small blood vessels, contributing to endothelial injury and vascular dysfunction. Deficient oxygen transport to tissues is a critical determinant of disease progression. Beyond changes in red cell shape, sickle cell disease is recognized as a systemic condition involving inflammation and blood vessel damage. Chronic red cell destruction depletes nitric oxide, promotes oxidative stress, stimulates the endothelium and sustains inflammatory signals. These mechanisms promote widespread tissue injury affecting the kidneys, lungs, spleen, bones and central nervous system (5&9). Clinically, SCD is characterized by both acute and chronic complications, including vaso-occlusive crises, acute chest pain and chronic organ damage. These complications arise from repeated episodes of blood vessel obstruction and ischaemia (reperfusion injury), leading to worsened complications and a shortened lifespan. (3). The severity of SCD is highly variable and is influenced by genetic and haematological modifiers, particularly fetal haemoglobin (HbF). HbF inhibits HbS

polymerisation by interfering with polymer formation, thereby reducing sickling and improving red cell survival. Higher HbF levels are strongly associated with milder disease expression and fewer vaso-occlusive crises (5&11). Globally, SCD remains a significant public health challenge, particularly in sub-Saharan Africa, where the burden is highest. Nigeria accounts for a large proportion of affected births annually. While improvements in screening, vaccination and therapies have enhanced outcomes, many resource-limited regions still lack access to optimal care. (9&17).

2.1 Vaso-Occlusive Crisis in Sickle Cell Disease

Vaso-occlusive crisis (VOC) is the most frequent and clinically significant acute complication of sickle cell disease (SCD). The condition is marked by episodes of severe pain caused by sickled red blood cells temporarily blocking the small blood vessels. VOC remains the primary cause of emergency hospital admissions and significantly contributes to morbidity, reduced quality of life and healthcare burden in affected individuals (3). The pathophysiology of VOC is initiated by the polymerisation of deoxygenated haemoglobin S (HbS), leading to red blood cell sickling. However, VOC is not just mechanical blockage. It involves a series of factors. Sickled erythrocytes exhibit increased tendencies to adhere to the vascular endothelium due to altered membrane properties. This promotes abnormal interactions between red blood cells and endothelial cells, initiating occlusion of micro blood vessels (14). Endothelial dysfunction is a major factor in vaso-occlusive crises. Ongoing haemolysis lowers nitric oxide levels, which leads to blood vessel narrowing, greater endothelial activation and higher expression of adhesion molecules. Together, these changes create an inflammatory and clot-promoting environment that encourages cell adhesion and vascular blockage (5&9). In addition to erythrocytes, leukocytes and platelets actively contribute to the vaso-occlusive process. Activated neutrophils adhere to the endothelium and interact with sickled red cells, amplifying vascular blockage. Platelet activation further promotes inflammation and coagulation, reinforcing the occlusive process. VOC is a multicellular process, shaped by complex interactions between blood cells and the vessel lining. (15). A critical feature of VOC is the role of inflammation and ischaemia–reperfusion injury. Initial vascular obstruction leads to tissue hypoxia, followed by reperfusion upon partial restoration of blood flow. This cycle generates reactive oxygen species, intensifies oxidative stress and worsens endothelial injury. Consequently, VOC is increasingly recognised as a self-perpetuating vicious cycle of inflammation, adhesion and vascular damage (3). HbF plays a protective role by inhibiting HbS polymerisation, thereby reducing red cell sickling and vascular obstruction. Individuals with higher HbF concentrations tend to experience fewer and less severe vaso-occlusive episodes. This biological connection is the foundation for treatments that work by raising HbF levels to change the course of the disease. (5&12). Clinically, VOC presents with severe pain episodes commonly affecting the long bones, chest, abdomen and back. These crises may be triggered by factors such as infection, dehydration, cold exposure, stress, or hypoxia. Recurrent episodes contribute to organ damage and impair the quality of life in affected individuals (9&17).

3. Fetal Haemoglobin and Disease Modulation

Fetal haemoglobin (HbF) is the predominant haemoglobin present during fetal life. It is composed of two alpha (α) and two gamma (γ) globin chains and is gradually replaced by adult haemoglobin after birth. Although HbF levels normally decline during infancy, its persistence in individuals with sickle cell disease (SCD) has been associated with reduced disease severity and improved clinical outcomes (1&8). HbF is widely recognised as the most important natural modifier of sickle cell disease. Evidence of its protective role is observed in infants with SCD, who are generally protected from severe disease manifestations during the first few months of life when HbF levels remain high. As HbF concentrations decrease after birth, symptoms such as painful vaso-occlusive crises and chronic haemolytic anaemia begin to emerge (8). This observation provides strong evidence that HbF plays a crucial role in modulating disease severity. The protective effect of HbF is primarily attributed to its ability to inhibit the polymerisation of deoxygenated haemoglobin S (HbS). In

sickle cell disease, HbS molecules polymerise under low oxygen tension, causing red blood cells to become rigid and assume a sickle shape. HbF does not participate in this polymerisation process and therefore interferes with the formation of HbS polymers. As a result, red blood cell sickling is reduced, leading to fewer vaso-occlusive events and less haemolytic damage (1&8). Beyond inhibiting HbS polymerisation, HbF improves the deformability of red blood cells and enhances their passage through small blood vessels. This promotes more efficient microvascular circulation and reduces the likelihood of vascular obstruction. (13) Reported that increased HbF levels are associated with improved blood flow, reduced blood viscosity and decreased inflammatory responses, all of which contribute to a lower risk of vaso-occlusive complications. Clinical studies have consistently demonstrated that patients with higher HbF levels experience a milder disease course than those with lower HbF concentrations. Increased HbF has been associated with fewer hospital admissions, reduced frequency of painful crises, lower incidence of acute chest syndrome and improved overall survival. Consequently, HbF is regarded as an important predictor of prognosis and clinical outcome in individuals with sickle cell disease (1). The distribution of HbF among red blood cells is also important in determining its protective effect, the protection depends not only on the total amount of HbF present but also on how evenly it is distributed among circulating erythrocytes(1). A more uniform distribution ensures that a greater proportion of red blood cells are protected against sickling, thereby reducing disease severity. Genetic factors significantly influence HbF production. Variations in genetic regulators such as BCL11A, HBS1L-MYB and regions within the β-globin gene cluster have been linked to differences in HbF expression among patients with SCD (8). These genetic differences partly explain the variability in clinical manifestations observed among affected individuals. In summary, HbF plays a vital role in reducing the severity of sickle cell disease through multiple mechanisms, including inhibition of HbS polymerisation, improvement of red blood cell deformability and enhancement of microvascular blood flow. Its ability to reduce vaso-occlusive complications and improve clinical outcomes has made HbF a major target for therapeutic interventions, particularly hydroxyurea therapy.

4. Hydroxyurea Therapy in Sickle Cell Disease

Hydroxyurea is the most widely used disease-modifying drug for sickle cell disease (SCD). Unlike drugs that target the symptoms of sickle cell (e.g. pain killers for chest pain), it targets the underlying mechanisms responsible for disease complications (5). Since its introduction, it has significantly improved disease management and remains the standard treatment for many patients worldwide (17). The principal therapeutic effect of hydroxyurea is its ability to increase the production of fetal haemoglobin (HbF). Hydroxyurea works by releasing nitric oxide into the body, signalling the bone marrow to activate the gamma gene, responsible for the production of fetal hemoglobin. Hydroxyurea also mildly suppresses the bone marrow, thereby forcing it to produce younger, more flexible red blood cells, which naturally produces more fetal hemoglobin. As discussed in the previous section, HbF inhibits the polymerisation of haemoglobin S (HbS), thereby reducing red blood cell sickling. Hydroxyurea stimulates the production of HbF-containing red blood cells, helping to reduce the harmful effects associated with sickle cell disease (1&8). In addition to increasing HbF levels, hydroxyurea exerts other beneficial effects. Studies have shown that the drug reduces the number of circulating white blood cells and platelets, both of which contribute to inflammation and vascular blockage in sickle cell disease. Hydroxyurea also improves blood flow and reduces the tendency of blood cells to adhere to the walls of blood vessels, thereby helping to maintain normal circulation (5). Another important benefit of hydroxyurea is its ability to improve the quality and flexibility of red blood cells. This allows the cells to move more easily through small blood vessels and improves oxygen delivery to body tissues. Consequently, hydroxyurea helps to reduce some of the physiological abnormalities associated with sickle cell disease (5). Despite its benefits, hydroxyurea therapy requires regular monitoring. The most common concern associated with treatment is bone marrow suppression, which may lead to reduced levels of white blood

cells, platelets or reticulocytes. For this reason, patients receiving hydroxyurea should undergo routine laboratory investigations (especially Full Blood Count) to ensure safe and effective treatment (17). However, when appropriately monitored, hydroxyurea is generally considered safe and well tolerated. Overall, hydroxyurea has transformed the management of sickle cell disease by addressing important mechanisms involved in disease progression. Through its ability to increase fetal haemoglobin production and improve blood cell function, it remains a cornerstone of modern sickle cell therapy and continues to play a vital role in patient care (15).

5. Clinical Impact of Hydroxyurea-Induced HbF on Vaso-Occlusive Crisis

The elevation of fetal haemoglobin (HbF) levels is clinically significant in SCD, with measurable benefits for patients. The frequency and severity of vaso-occlusive crises (VOCs) tend to decrease significantly with the induction of fetal haemoglobin (5). Clinical trials have confirmed this relationship. The landmark Multicenter Study of Hydroxyurea (MSH) showed that adults with sickle cell disease who took hydroxyurea experienced about half as many painful crises as those who received a placebo. Specifically, the median number of crises per year dropped from 4.5 to 2.5 (2). The same study also found that hospitalisation rates fell and the risk of acute chest syndrome which is a serious lung complication was reduced by nearly 50% (2). These benefits are not only seen in adults. The BABY HUG trial, which studied children as young as nine months, demonstrated that hydroxyurea reduced pain episodes, hand-foot syndrome (dactylitis) and the need for blood transfusions and hospital admissions (16). Early treatment appears to make a meaningful difference in young lives. Long-term follow-up studies have provided further reassurance. Patients who stay on hydroxyurea for many years not only continue to experience fewer crises but may also have better survival rates compared to those who do not take the drug consistently (13&17). In essence, the clinical impact of hydroxyurea-induced HbF is clear: fewer pain episodes, fewer hospital visits and a lower chance of life-threatening complications. For many patients, this means more days spent at home, at school, or at work — and fewer days lost to pain and suffering (5&8).

6. Benefits and Limitations of Hydroxyurea Therapy

Hydroxyurea remains the most established disease-modifying therapy for sickle cell disease (SCD), with strong evidence supporting its ability to reduce disease severity through induction of fetal haemoglobin (HbF). Increased HbF inhibits haemoglobin S polymerisation, thereby reducing erythrocyte sickling and vaso-occlusion. Clinically, this translates into fewer vaso-occlusive crises, reduced hospitalisations and improved overall disease stability (7&12). Despite these benefits, response to hydroxyurea is not uniform across all patients. Variability in HbF induction and clinical response is well documented and is influenced by biological and pharmacokinetic differences, including genetic factors such as BCL11A polymorphisms. This necessitates careful dose adjustment and regular monitoring to achieve optimal therapeutic effect (6&11). Adverse effects are generally mild and reversible but may include bone marrow suppression, resulting in neutropenia, thrombocytopenia, or a temporary reduction in haemoglobin levels. These effects require routine full blood count monitoring to ensure safe long-term use. Other side effects, such as gastrointestinal discomfort, are usually transient and rarely necessitate discontinuation of therapy (7). In resource-limited settings such as Nigeria, additional challenges include limited access to monitoring facilities, inconsistent drug availability and socioeconomic barriers affecting adherence. These factors reduce the real-world effectiveness of hydroxyurea despite its well-established clinical efficacy (5). Overall, hydroxyurea remains a highly effective therapy for SCD, with proven benefits in reducing morbidity and improving quality of life. However, its success depends on appropriate monitoring, dose individualisation and healthcare system support, particularly in low-resource settings.

7. Discussion

The aim of this seminar was to understand how hydroxyurea induced fetal haemoglobin (HbF) prevents vaso occlusive crisis (VOC) in sickle cell disease. The literature reviewed provides a clear answer. Hydroxyurea raises HbF levels and HbF directly interferes with the polymerisation of haemoglobin S. When polymerisation is reduced, red blood cells are less likely to sickle and fewer sickled cells mean fewer blocked blood vessels and fewer painful crises (1&8). This mechanism is well established and explains why hydroxyurea has remained the standard of care for decades. The literature reviewed demonstrates that sickle cell disease (SCD) is a multisystem genetic disorder arising from a point mutation in the β-globin gene, which results in the production of haemoglobin S (HbS). However, the literature also shows that the relationship between HbF and clinical improvement is not identical for every patient. Some individuals achieve high HbF levels and experience a drastic reduction in pain episodes, while others respond more modestly. Genetic factors, particularly variations in the BCL11A gene, account for much of this variability (8). This means that a patient's genetic makeup partly determines how well hydroxyurea will work. While genetic testing is not yet routine in most clinical settings, recognizing this variability helps manage patient expectations and reinforces the need for careful dose adjustment. A closer look at the literature also reveals that HbF does not explain all of hydroxyurea's benefits. Beyond HbF induction, hydroxyurea also reduces leukocyte and platelet activity, thereby decreasing endothelial adhesion and inflammatory activation. These combined effects contribute to improved blood flow and reduced vaso-occlusive crises (5). These effects are independent of HbF and are clinically significant because a patient with only a modest rise in HbF may still experience fewer crises.

Another important point raised by this review is the gap between clinical trial results and everyday practice. The MSH trial and the BABY HUG trial proved that hydroxyurea can dramatically reduce VOCs under ideal conditions (with regular monitoring, guaranteed drug supply and motivated participants) (2&16). In many Nigerian hospitals, however, consistent laboratory monitoring is not available. Some patients cannot afford transport to the clinic or purchase the drug itself. These logistical barriers mean that a drug with proven efficacy may still fail in real world settings (5). This disconnect is not a failure of the drug but a failure of the systems that support its use. In summary, hydroxyurea prevents VOC through HbS polymerisation inhibition and secondary anti-inflammatory effects. However, in Nigeria and other developing countries, its real-world success depends less on biology and more on whether health systems can support safe, consistent use.

8. Conclusion

Hydroxyurea prevents vaso-occlusive crises in sickle cell disease primarily by increasing fetal haemoglobin, which inhibits HbS polymerisation and reduces red blood cell sickling. Its additional effects on leukocytes, platelets and endothelial function provide further protection against vaso-occlusion and inflammation. This directly addresses the central focus of the review. However, the literature also shows that scientific efficacy alone is insufficient to achieve optimal outcomes. In Nigeria and other resource-limited settings, systemic challenges such as inconsistent drug availability, limited access to laboratory monitoring and socioeconomic constraints significantly limit the real-world impact of hydroxyurea therapy. While the drug is effective, its full benefit depends on the strength of the healthcare systems in which it is implemented.

9. Recommendations

The following recommendations are offered to improve the use of hydroxyurea in preventing vaso-occlusive crises, particularly in resource-limited settings such as Nigeria.

Expand access to hydroxyurea: The drug should be made available in all secondary and tertiary health facilities managing SCD patients. National sickle cell programmes should prioritise consistent supply chains to prevent stock outs.

Strengthen laboratory monitoring: Basic full blood count monitoring is essential for safe dose adjustment. Investment in

point-of-care haematology analysers and regular quality control should be prioritised in under-resourced hospitals.

Train healthcare workers: Clinicians and nurses need practical training on hydroxyurea dosing, monitoring schedules and recognition of side effects. Task-sharing with community health workers could improve follow-up for patients in remote areas.

Support patient adherence: Transportation subsidies, appointment reminders and patient education materials in local languages may help reduce dropout rates. Families should understand that hydroxyurea is a long-term therapy, not a crisis-only treatment.

Consider genetic screening where feasible: While not yet routine, testing for BCL11A polymorphisms could help predict response and set realistic expectations. Research into cost-effective screening approaches in African populations is needed.

Encourage further research: Local studies on hydroxyurea effectiveness, adherence barriers and simplified monitoring protocols in Nigerian settings would help bridge the gap between clinical trial evidence and real-world practice.

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